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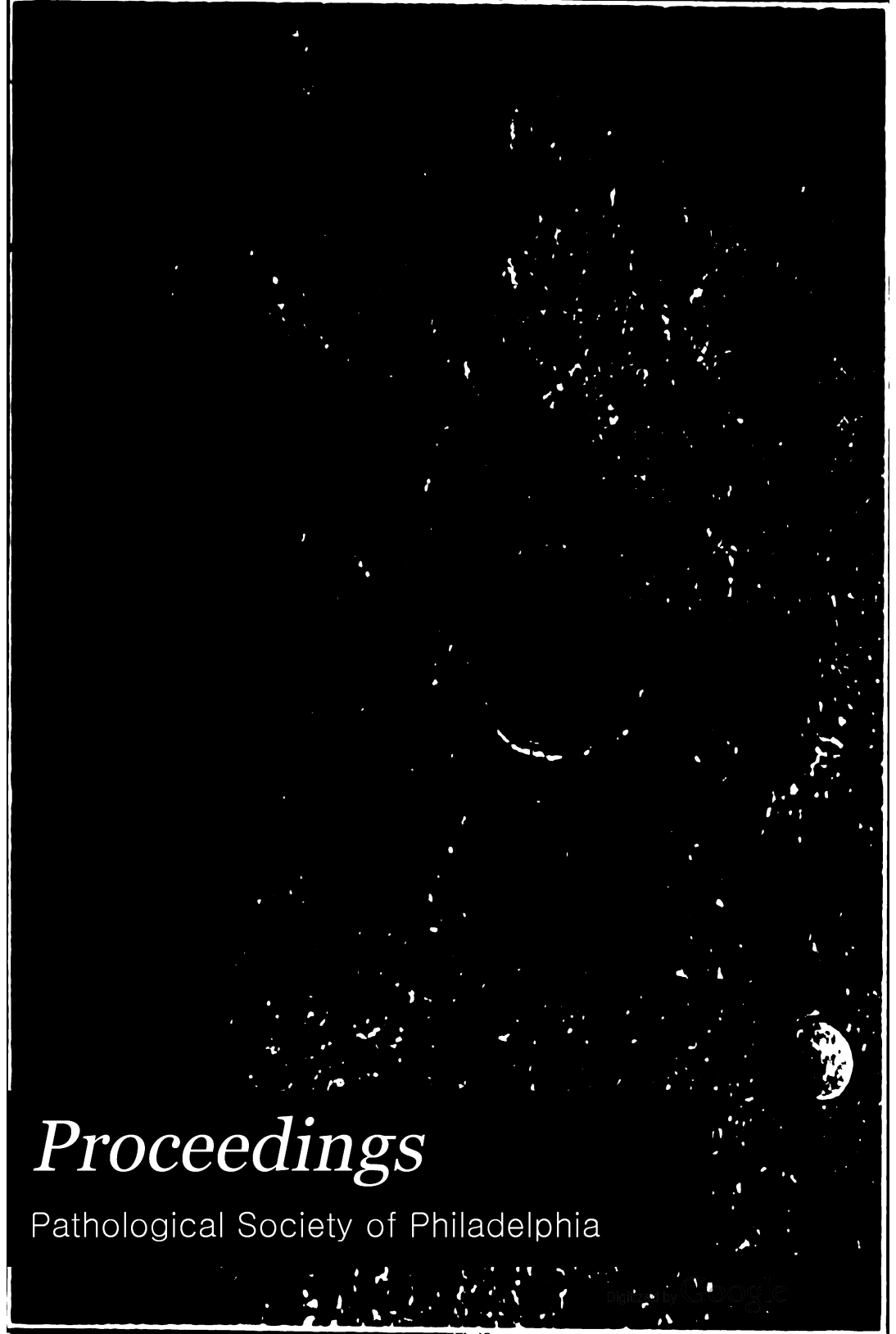

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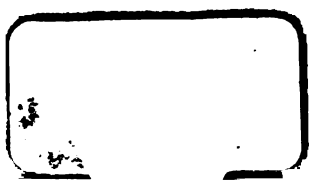

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OF THE

PATHOLOGICAL SOCIETY

OF PHILADELPHIA

NEW SERIES, VOLUME XII
OLD SERIES, VOLUME XXX

CONTAINING THE TRANSACTIONS OF THE SOCIETY FROM SEPTEMBER, 1908, TO JUNE, 1909

EDITED BY

FRED H. KLAER, M.D.

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1866 Duer, Edward L., 1606 Locust Street.
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1870 Henry, Frederick P., 114 S. Eighteenth Street.
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1878 Mills, C. K., 1909 Chestnut Street.
1884 Mitchell, J. K., 1730 Spruce Street.
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1869 Stryker, Samuel S., 3833 Walnut Street.
1863 Tyson, James, 1506 Spruce Street.
1887 Westcott, T. S., 1720 Pine Street.
1873 White, J. William, 1810 South Rittenhouse Square.
1868 Willard, De Forest, 1901 Chestnut Street.
1869 Wilson, James C., 1509 Walnut Street.
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1887 Berens, Bernard, 2041 Chestnut Street.
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1887 Burr, Charles W., 1327 Spruce Street.
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1907 Cadwalader, W. B., 1710 Locust Street.
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1902 Carncross, H. L., 721 Pine Street.
1903 Carnett, J. B., 318 South Fifteenth Street.
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1902 Carpenter, H. C., 1805 Spruce Street.
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1887 Cattell, H. W., 3709 Spruce Street.
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1909 Hammond, L. J., 1222 Spruce Street.
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1904 Hatfield, C. J., 2008 Walnut Street.
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1900 Head, J., 1500 Locust Street.
1896 Henry, John N., 114 South Eighteenth Street.
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1899 Hitchens, A. P., Glenolden, Pa.
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1890 Laplace, Ernest, 1828 South Rittenhouse Square.
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1888 Leidy, Joseph, 1319 Locust Street.
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1903 Rhein, R. D., 2016 Pine Street.
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1895 Sailer, Joseph, 1830 Spruce Street.
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1898 Sharpless, Wm. T., 100 South Church Street, West Chester, Pa.
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1889 Shoemaker, Harvey, 2011 Chestnut Street.
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1902 Sinkler, Francis W., 220 South Sixteenth Street.
1901 Siter, E. H., 2038 Locust Street.
1903 Small, J. H., 914 South Forty-eighth Street.
1903 Smith, A. J., Medical Department, University of Pennsylvania.
1897 Smyth, Henry Field, Odessa, Delaware.
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1906 Sommers, Henry J., Blair County Hospital for Insane, Hollidaysburg, Pa.
1905 Speese, John, 248 South Twenty-first Street.
1893 Spellissy, Joseph M., 110 South Eighteenth Street.
1896 Spiller, William G., 4409 Pine Street.
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1890 Stahl, B. F., 1727 Pine Street.
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1908 Starkey, Frank R., 445 South Forty-fourth Street.
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1899 Talley, J. E., 1927 Chestnut Street.
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1894 Thomas, W. Hersey, 1421 North Seventeenth Street.
1902 Thornton, E. Q., 1331 Pine Street.
1909 Tint, J. Louis, Philadelphia Hospital.
1902 Tracy, S. E., 1429 Spruce Street.
1897 Tucker, Henry, 112 South Twentieth Street.
1890 Tyson, T. Mellor, 1506 Spruce Street.

1900 Uhle, A. A., 1327 Jefferson Street.
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1894 Vandervoort, C. A., 3311 North Broad Street.
1909 Van Gasken, Francis C., 115 South Twenty-second Street.
1909 Vaux, Norris Wister, Chestnut Hill, Phila.
1909 Veeder, Borden S., 2033 Locust Street.

1891 Wallace, James, 1921 Chestnut Street.
1899 Walsh, J., 732 Pine Street.
1903 Weisenburg, T. H., 2030 Chestnut Street.
1908 Weston, Paul G., 1632 Green Street.
1897 White, Courtland Y., 1808 Diamond Street.
1901 Whiteway, Harold M., 1924 Chestnut Street.
1893 Whiting, A. D., 1523 Spruce Street.
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1898 Willson, R. N., Jr., 1708 Locust Street.
1906 Wilson, J. D., Jefferson Medical College.
1907 Wilson, Oscar H., 5128 Spruce Street.
1891 Wilson, Samuel M., 1517 Arch Street.
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1900 Wister, J. W., 5430 Germantown Avenue.
1890 Wood, A. C., 128 South Seventeenth Street.
1898 Wood, George B., 129 South Eighteenth Street.
1906 Wood, Harold B., 5038 Pine Street.
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McConnell, G., 4175 Washington Avenue, St. Louis, Mo.
Pearce, Richard M.,
Rahter, C. A., 110 North Second Street, Harrisburg, Pa.
Ravenel, M. P., University of Wisconsin, Madison, Wis.
Royer, B. Franklin, Donaldson Bldg., Harrisburg, Pa.

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Egbert, Joseph C., Wayne, Pa.
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Gerson, T. P., 1621 Ingraham Street, Los Angeles, Cal.
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Kinyoun, J. J., 1423 Clifton St., Washington, D. C.
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de Nancrède, C. B. G., Ann Arbor, Mich.
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Powell, W. M., 122 West Minor Street, West Chester, Pa.
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Williams, H. L., 327 Fourteenth Ave., S. E., Minneapolis, Minn.
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Report of a Case of Metastatic Carcinoma of the Lung, with Pathological Findings.

BY GEORGE WILLIAM NORRIS, M.D.

THE patient, a multipara, aged forty years, presented herself for examination on June 12, 1908, believing that she was suffering from pulmonary tuberculosis. The first symptoms had appeared three months previously. At the time of my examination she gave a history of emaciation (thirty pounds), cough, dyspnea, night sweats, anorexia, asthenia. Her right breast had been amputated four months before.

PHYSICAL EXAMINATION. Extreme dyspnea, nearly to the point of syncope, after ascending one flight of stairs; ashen pallor; cyanosis; emaciation. Cardiac dulness enlarged to the right. Impaired pulmonary resonance over the upper right chest anteriorly, with tactile fremitus, vocal resonance, bronchial breathing, and moist rales over the same area. Exaggerated breath sounds over the left chest. Posteriorly there was bilateral hyper-resonance, with scattered moist rales and stridulous breath sounds. The liver extended slightly

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below the costal margin. The patient seemed in too critical a condition for a more prolonged examination, and was advised to enter the University Hospital, which she did the next day.

A diagnosis of metastatic carcinoma of the lung and probably of the liver was made at this time, based upon the following reasoning: (1) The history of breast amputation a few months before. (2) The dyspnea, cyanosis and distress were entirely out of proportion to the apparent extent of the pulmonary lesion—for a case of pulmonary tuberculosis. (3) The wasting of the tissues was not nearly so great as is the case in advanced tuberculosis. (4) The physical signs pointed more to pressure on the bronchi than to destruction of lung tissue.

The case was admitted to the University Hospital (service of Dr. Stengel), and died five hours later.

The report of the autopsy, performed by Dr. Karsner, is as follows: *Lungs:* Metastatic carcinoma of lungs. *Heart:* Cloudy swelling of myocardium, dilatation. *Liver:* Metastatic carcinoma, congestion, cloudy swelling; pancreas, slight chronic interstitial pancreatitis; spleen, acute splenic tumor; adrenals, postmortem degeneration; kidneys, acute parenchymatous nephritis; stomach, chronic hypertrophic gastritis; arteriosclerosis, uterus, etc., acute catarrhal endometritis, left-sided varicocele, cervical laceration and erosion. *Lymph glands:* Metastasis from tumor in mediastinal and bronchial glands.

Detailed Autopsy Report (Dr. Karsner).

General. Body of a fat, short-statured, adult white woman, showing complete absence of right breast and a healed linear incision extending over right chest from a point near the junction of the sternum and the eighth rib, diagonally up to the shoulder, and out on the upper arm. Rigor mortis moderate; lividity slight; no distinct cyanosis. Primary incision shows a thick panniculus adiposus and pallid musculature. Superficial lymphatics not enlarged.

Abdomen. Abdominal cavity contains markedly distended intestines; liver which extends 1 cm. below the costal margin in midclavicular line, and an appendix which points downward and inward, hanging over the brim of the pelvis, and normal position of other viscera; smooth, glistening peritoneum; small amount of cloudy, brownish fluid in pelvis. Omentum shows markedly distended veins.

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Spleen weighs 100 gm.; measures 12.5 x 8.5 x 2.5 cm.; shows slightly thickened and opaque capsule; cuts with ease; shows a soft, semifluid, dark red pulp, in which the follicles can be seen as large gray bodies; trabeculæ almost completely obscured.

Left adrenal normal in size and shape; cuts with diminished resistance; shows a firm yellow cortex and a fluid, dark brown medulla.

Left kidney weighs 160 gm.; measures 12.5 x 5 x 3.5 cm.; capsule strips with ease; leaves a bluish brown and smooth, moist outer surface showing moderate fetal lobulation; stellate veins moderately distended. Organ cuts with ease; shows a bulging, bluish brown, bleeding, soft cut surface; cortex 7 mm. in width, shows diminution in striation caused by increase in width of the lighter striæ; glomeruli can be made out as fine bright red pin-points; entire substance measures 2.2 cm.; pyramids are injected, purple in color; peripelvic fat moderate in amount. Pelvis shows an injected mucosa.

Right adrenal is like its fellow.

Right kidney weighs 140 gm.; measures 12 x 5.5 x 3 cm.; cortex measures 7 mm.; entire substance, 2.4 cm.; otherwise answers to the same description as that given for its fellow.

Bladder contains a small amount of cloudy yellow urine; mucosa normal.

Uterus is in normal position; 6.5 cm. long by 5 cm. in width at the fundus; cervix shows a stellate tear and some loss of epithelial covering extending upward into the cervical canal. The fundus shows an intensely congested, thickened mucosa; cavity contains a small amount of cloudy, white, viscid material very suggestive of pus. Right tube measures 13.5, the left 10 cm. in length; both are of normal caliber, moderately congested, have free fimbriated extremities, and apparently normal mucosa. Pampiniform plexus on the left side shows marked distention and corrugations of the veins. Both ovaries are small, firm, and wrinkled. No enlargement of retroperitoneal, pelvic, or mesenteric glands.

Liver weighs 2650 gm.; measures 31 x 23.5 x 7 cm.; is of normal shape, and shows a smooth, glistening, transparent capsule, through which can be seen numerous slightly projecting gray nodules, generally circular in shape, having a diameter varying from 2 to 12 or

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14 mm.; in the anterior margin one nodule shows distinct central retraction. The organ cuts with ease; shows a slightly bulging, slightly bleeding, bluish brown cut surface, in which the lobular structures can be seen very distinctly; central portions of the lobules are deep reddish brown in color, peripheral parts forming a network of grayish brown. Throughout the cut surface can be seen a moderately large number of nodules corresponding to those seen on the surface in appearance, the cut surface showing no distinct structure, being of a grayish color, homogeneous, without evidence of necrosis; in a few can be seen central depressions which are yellowish-red in color.

Gall-bladder is filled with viscid, yellowish-green bile; mucosa normal; bile ducts patulous.

Pancreas measures 21 cm. in length; proportionately broad and thick; cuts with slightly increased resistance; shows distinctly lobulated yellowish-gray surface, with moderate interlobular congestion.

Stomach measures 12 x 23 cm.; is distended with gas, and with a moderate amount of cloudy, granular, brownish-yellow fluid. Mucosa is thickened throughout and thrown into minute folds, giving it a mosaic-like appearance; congestion is marked throughout, in some areas going on to the production of minute submucous hemorrhages. The wall as a whole is not increased in thickness.

Intestines. Both small and large show slight submucous congestion.

Appendix measures 6 cm. in length; patulous throughout.

Right pleura is smooth and glistening throughout; right chest wall shows no tumor involvement whatever.

Right lung weighs 1370 gm.; shows a smooth, glistening, transparent pleura, through which can be seen numerous coalescing nodules, somewhat similar in appearance to those seen in the liver; between these nodules can be made out emphysema, varying in degree from slight distention of the vesicles to distinct bullæ. Organ cuts with slightly increased resistance, and shows a gray, moist, cut surface, becoming red toward the base. Throughout the upper, middle, and lower lobes can be seen numerous gray nodules varying in size and shape; in some cases discrete, in other cases conglomerate; show no depression of the central portions and no necrosis; the margins are not

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sharply outlined, and they fade off into the surrounding tissue; the color is very suggestive of that of gray hepatization, but close inspection shows a distinct tinge of yellow. These nodules show no structure whatever; they vary in size from a few millimeters in diameter to 4 or 5 cm., and involve more extensively the upper and middle than the lower lobes. The healthy lung shows slight congestion, moderate pigmentation, and emphysema corresponding to the appearance seen on the pleural surface. Careful examination of the bronchi shows slight thickening and a small amount of mucus and distinct congestion; but no tumor formation. Vessels are normal. Peribronchial glands enlarged, pigmented, contain small tumor nodules.

Left pleura is like the right.

Left lung weighs 1190 gm.; shows a focal area of increased thickness of pleura without any corresponding appearance on the parietal pleura. In other respects it is like its fellow. The superior mediastinal and tracheal glands show moderate enlargement, pigmentation, and the presence of pea-sized to marble-sized nodules.

Pericardium surfaces smooth and glistening; cavity contains about 20 c.c. of clear yellow serum.

Heart weighs 360 gm.; about the size of the patient's clinched fist, soft and flabby; shows a moderate amount of subepicardial fat; muscle cuts with ease and shows a grayish-brown bulging, friable, slightly bleeding cut surface; left ventricular wall measures 12 mm.; left auriculoventricular orifice, 10.5 cm.; leaflets slightly thickened; chordæ tendineæ normal. Aortic orifice measures 6.5 cm.; shows moderate thickening of the leaflets, particularly about the bases, and very slight sclerosis of the sinuses of Valsalva, this not involving the coronary orifices; ventricular cavity moderately enlarged, shows some flattening of the columnæ carneæ. Right ventricular wall measures 3.5 mm; right auriculoventricular orifice, 12 cm.; leaflets normal. Pulmonic orifice, 7 cm.; leaflets of normal thickness, but there is an additional small cusp located between the posterior and right anterior leaflets, making four in all; ventricular cavity is slightly distended and shows some flattening of the columnæ carneæ. Auricular cavities normal.

Aorta shows a few very small, slightly elevated plaques of thickening and yellowing of the intima.

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Discussion.

Dr. H. R. M. Landis: The following case was admitted to the Phipps Institute September 20 and died two days later:

Female, aged forty-nine years, white. Father and mother died at the age of seventy-two, both of old age. One brother died of Bright's disease, one was killed accidentally, and one died of "miner's asthma." One sister died in confinement, and two sisters are living and well.

Aside from measles and whooping cough in childhood, she had always enjoyed good health; was married and had three living children. She had also miscarried twice.

Present illness began six months ago with pain in the precordium. Although she had lost about twenty pounds within the past six months, she still presented the appearance of a well-nourished woman, inclining to stoutness.

In addition to the precordial pain, she had a severe cough, equally severe both day and night, profuse yellow expectoration and marked orthopnea, the latter having appeared three weeks previously. The temperature was subnormal in the morning and 99° in the evening; pulse, 90 to 110; and the respirations, while not exceeding 32, were very labored.

The one examination made of the sputum was negative for tubercle bacilli. The urine contained neither albumin, sugar, nor casts.

The examination was very unsatisfactory, owing to the patient's illness and her inability to assume anything but a sitting posture. This latter factor and the thickness of the abdominal wall rendered the examination of the abdomen useless. She was extremely cyanosed, and the breathing was very labored.

The heart was enlarged slightly to the right; the pulmonic second sound was accentuated; no murmurs.

The lungs gave an impaired percussion note over both upper lobes and a hyperresonant note below. The breathing was harsh and asthmatic in character, and numerous large and small rales were heard over both lungs. There were no localizing signs.

Owing to the cyanosis, extreme dyspnea, precordial pain, enlarge-

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ment of the heart to the right, and the negative sputum examination, a tentative diagnosis of dilated heart was made, although this was not satisfactory, owing to the comparatively slow pulse and the negative urinary findings.

Autopsy. At the autopsy a small hard nodule the size of a walnut was found in the left breast. This was the primary growth and proved microscopically to be a scirrhus carcinoma.

The left pleura was thickened at the apex, but not adherent. The right pleura showed a few fine adhesions at the apex. Both pleural sacs had a slight excess of bloody serum.

The Left Lung. The external surface was deeply grooved. The cut surface showed numerous firm, whitish nodules, 1 to 3 cm. in diameter. The nodules were more numerous in the upper lobe. The lower lobe, in addition to a few nodules, was congested and emphysematous.

The nodules in some instances showed elevation of the margins above the surrounding tissue and the centres were depressed.

The right lung showed similar changes.

The pericardium contained a slight excess of fluid.

The right ventricle and auricle were slightly dilated.

The liver was dark red in color and weighed 1575 grams. The external surface showed scattered round nodules measuring from 3 mm. to 3 cm. in diameter. Some of the nodules were distinctly umbilicated. On section the surface was studded with nodules, one measuring 5 by 4 cm.

The spleen contained one nodule measuring 1 by 0.75 cm.

The kidneys showed cloudy swelling.

The absence of cachexia, small loss of weight, cyanosis, and marked dyspnea present in this case were quite characteristic of metastatic carcinoma of the lung.

The point of special interest was the presence of the primary growth in the left breast, which gave rise to pain.

The failure to examine the breasts in this case led to a mistaken diagnosis, and emphasizes the importance of examining these organs in obscure conditions affecting women.

DR. J. ALISON SCOTT: I have been impressed with the difficulty of diagnosis in primary growths of the lung as compared with the

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secondary growths. During the past several years two or three cases of primary growth of the lung have been seen at the University Hospital. In one of these cases the behavior of the symptoms of the patient was such as to make the attending physician suspect loculated empyema. The man presented temperature, toxicity, and a recurring pleural effusion. Not until an exploratory resection of the rib was done was the diagnosis of malignant disease of the lung and pleura suspected. At subsequent autopsy numerous white nodules varying in diameter from ¼ to 2 cm. were found in the pleura, as well as an area near the base of the right upper lobe of intense white infiltration which surrounded a large vein and bronchus. In these cases pain was not complained of except very early in the disease. There was practically no expectoration. *October* 16, 1908.

Report of a Case of Malignant Tumor of the Testicle Resembling Chorio-epithelioma, with Metastasis.

By J. A. SCOTT, M.D., and WARFIELD T. LONGCOPE, M.D.

(From the Ayer Clinical Laboratory, Pennsylvania Hospital.)

H. B., aged forty-five years, a clergyman and editorial writer, was admitted to the private rooms of the Pennsylvania Hospital on January 30, 1904, complaining of cough, dyspnea, and general weakness of two months' duration. His family history shows nothing of importance. There is no history of tuberculosis or malignant disease.

Past History. During childhood, and especially during the past five years, he has had repeated attacks of malaria(?). He has never been strong and has had several indefinite illnesses, one a rheumatic attack followed by pericarditis some time in the nineties; in 1899, after a serious strain, he became nervously exhausted, had to give up his parish and since then has not been strong. His digestion has been fickle, bowels constipated; he thinks his heart has been weak; he has been considered anemic or lithemic and within recent months has been depleted, bathed, and dieted rather rigidly. No mental

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disturbance. No definite symptoms until the beginning of this illness.

The *present illness* began in November 1903 (though his friends had considered his health failing for a year or more before this) with pain in the right thigh and in the sciatic area—rather severe, and more or less constant. Shortly before this time he began to cough, and this has continued; at first dry, but now and then accompanied with a small quantity of blood-stained sputum. He has had neither hemorrhages nor fever, and his weight and strength have been considerably reduced in the last few weeks. He has dyspnea and sleeps but little at night. He complains of no pain except in the sciatic region.

Physical Examination. A spare, sandy-haired, freckled man, with rather anxious expression. A shadow of blueness in lips and finger nails, decidedly anemic in appearance. The eyes are normal. Tongue heavily coated and pale. The chest flat and narrow and expands fairly well, somewhat better on right than on the left side. The percussion note seems hyper-resonant on both sides. Over the anterior surface of the left lung, fine crepitation can be heard with inspiration. Now and then present also with expiration. (This was regarded as pleural.) Sounds found in the right lung are well heard; expiration is somewhat prolonged. The area of cardiac dulness is decidedly reduced and the sounds at all areas are clear, but not strong. Liver and spleen normal in size. Abdomen rather flat, but soft. There is some resistance in the epigastric region and palpation is not satisfactory. (Nothing abnormal was felt, however, at any time.) The legs are thin. There is no tenderness in the right sciatic area, nor is anything abnormal noted in either extremity.

The urine showed specific gravity 1024, pale amber, clear, without sediment and contained neither albumin nor sugar. On microscopic examination, three or four hyaline casts were found. The genitalia were not examined. The sputum was vicid, scanty, and now and then contained rather dark blood in small quantities. No tubercle bacilli were present and no other organisms were noted.

Examination of the blood showed erythrocytes, 2,272,000; leukocytes, 11,400; hemoglobin, 47 per cent. The temperature was usually a few points above normal, and on only one occasion rose to 100°;

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it was sometimes subnormal. Respirations were always rapid, being 28 and above.

After several days' study of his physical signs, no definite diagnosis was made. It was believed he had a dry pleurisy and probably tuberculosis of the left lung, though there were many signs wanting to establish such an opinion. During his two weeks stay in the hospital the dyspnea increased, and owing to a dry hacking cough he slept but little. There was nothing to call attention to the rectum, bladder, or the abdomen. The bowels were constipated moving every two days with laxatives. Rales, crepitant and crackling, first became evident over the entire left lung and then at the right base; the respirations became less frequent, the face drawn and sunken, the pulse very weak and rapid, and the temperature subnormal. At no time did he complain of pain. He became delirious on the day of his death, and early in the afternoon his hands and feet became cold and he died at 7.30 P.M., February 15.

The actual cause of his death could not be decided upon. It seemed clear that he did not have tuberculosis. Malignant disease with metastasis to the lung was not considered.

AUTOPSY ABSTRACT, FEBRUARY 16, 1904.

Anatomical Diagnosis. Tumor of right testicle, metastases to retroperitoneal lymph nodes; rupture into inferior vena cava; secondary growths in lungs, liver, myocardium, spleen, kidneys, stomach, and intestines; anemia of all organs.

The left testicle is exceedingly small and soft, being little larger than an almond. It lies just inside the internal abdominal ring, upon the parietal peritoneum above the psoas muscle, and almost beneath Poupart's ligament. In the right side of the pelvis there is a large lobulated tumor mass which is adherent to both bladder and rectum, but is not adherent to the parietal peritoneum covering the pelvis. It appears to hang by a pedicle which is apparently formed by the spermatic cord and accompanying vessels. The pedicle emerges from the internal abdominal ring and makes a half-twist before reaching the tumor. The length of the pedicle is 3 cm.

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Lungs. Left lung is very large and heavy; it has three lobes. Over the posterior surface of the upper lobe there is a raised, ragged, bloody area about 5 cm. in diameter where the adherent lung was torn from the chest wall. Elsewhere the pleura is smooth, glistening, and free from adhesions. The color is mottled purple, gray, and red. The lung has an extremely irregular nodular appearance. On palpation it is found to be filled with hard nodules which seem to vary from the size of a pea to the size of a walnut. They are very numerous and the nodular appearance is due to the fact that the masses near the surface are highly raised. On the pleural surface they appear red or purplish, and over the largest ones the pleura has a granular look. Between them the lung tissue appears insufflated, pale, and the air vesicles are greatly distended. The cut surface of the lung presents a very remarkable appearance. The entire lung from anterior margin to posterior border is simply filled with nodular masses. They vary from 1 to 2 mm. to 3 to 4 cm. in diameter. They also vary a good deal in color and consistency. The smaller ones are pale gray or reddish gray and very firm. The larger ones are deep red to purple and are firm about the periphery, but often softened in the centre. In cutting through some of them fluid blood escapes from the central portion, leaving a large ragged cavity wall behind. These nodules are very peculiar in that they are absolutely circumscribed and almost perfectly round. Although they are quite hard they have a friable consistency. Between them the lung tissue seems depressed and is pale gray or red in color. In places it is insufflated, but toward the posterior part it is very moist, exudes fluid, and here and there are patches which do not contain air. Some of the larger bronchi lead directly into the softened bloody centres of the largest nodules. The vessels at the root contain firm, dark-red, postmortem clots. The bronchi are pale and clear. The vessels, followed out for some distance into lung tissue, show no direct connection between them and the growths.

The right lung shows four lobes and presents almost the same appearance as the left, except that the nodules are not quite so large, and the lung tissue between them shows rather an extensive consolidation which is quite moist and generally pale gray in color, although immediately about some of the nodules it has a yellowish appearance.

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Bronchi at the root pale. Vessels contain postmortem blood clots. Similar nodules are found in the spleen, liver, kidneys, stomach, and intestines.

Urinary bladder, *prostate*, and *seminal vesicles* apparently normal; the vas deferens on the left side gradually narrows in caliber from the ampulla toward the testicle, until at the testicle it is completely occluded. The left testicle is quite soft and is about the size of an almond. On section it has a peculiar greenish color and is studded with small, opaque, white or yellow points. The epididymis is greatly atrophied. The hernial sac contains the vessels and the atrophied vas. The mass which takes the place of the testicle on the right side appears about the size of an orange. It is lobulated in appearance and has a somewhat oval shape, suggesting the appearance of the normal testicle. Except where it is adherent to the posterior portion of the bladder and rectum it is covered by a smooth serous membrane, below which many large dilated veins are seen. The vas deferens, which is practically occluded throughout its length, together with the vessels of the spermatic cord, run for some distance over one part of the tumor and fuse with the serous covering. The tumor is mottled extensively deep purple, red, yellow, and gray. Where the attachment to the bladder is loosened a torn, friable, yellow surface is exposed. The tumor measures approximately 11 cm. in length by 7½ cm. in width by 5 cm. in thickness. The cut section exposes a surface cut up into three more or less definite parts: an upper, lower, and triangular middle part. The upper part is deep purplish red, fairly firm, and looks a good deal like the tumors in the lung. The middle part is mottled gray and red, with here and there yellow areas. It apparently has quite a complicated structure and hard portions alternate with soft necrotic areas, and with raised red nodules. Here and there a few small cysts are seen. The lower part appears even more complicated. It is made up of soft yellow parts, white and red nodules, necrotic areas, and cysts sometimes from 1 to 1½ cm. in diameter.

Retroperitoneum. Just beneath the head of the pancreas a large, irregular, lobulated mass is seen in the retroperitoneum. It is more or less round, about 6 cm. in diameter, and purple in color. On section it has the appearance of a mass of nodules from the lung.

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It lies between the aorta, which is pushed somewhat to the left, the growth extending to the vertebral column and the inferior vena cava, which is pushed upward and to the right. On opening the inferior vena cava it is found to be filled with a firm, red, postmortem clot. The clot is sprinkled with tiny red and yellow points. The clot is adherent to a purplish mass about 2 cm. in diameter, which projects directly into the lumen of the vein from the underlying red tumor mass. Directly surrounding this large mass smaller nodules give the lining of the vessel an irregular granular appearance. Just below this the intima is much thickened and the vessel is narrowed. The iliac veins contain firm, red, postmortem clots. Just above the bifurcation of the aorta there is a round whitish nodule in the retroperitoneum, which on section appears to be made up of several cysts separated by soft yellowish material. It measures 2 cm. in diameter.

In the present case both testicles were undescended, the right being the seat of the tumor. In the retroperitoneum large masses were found which in structure and appearance were very much like the tumor of the testicle. From the retroperitoneum the growth had invaded and broken into the inferior vena cava, whence particles were swept to the lungs, finally entering the general circulation and giving rise to secondary nodules in almost every organ of the body.

Microscopic examination of many different portions of the testicular tumor showed blood, fibrin, and necrotic material, but only one variety of growth. The vast majority of cells forming this growth resembled very closely the Langerhans cells of the chorionic villi, while here and there a few multinucleated cells or syncytial masses were seen. Neither the remains of the testicle nor any of the usual structures seen in a teratoma could be discovered. The metastases were identical with what Marchand has termed the "typical form," of chorio-epithelioma. The lodgement of the secondary deposits and their subsequent growth through the walls of the bloodvessels could be beautifully traced in many of the smallest metastases

The nature of these growths is as yet disputed. Schlagenhaufer, in the light of Wilm's work upon the embryomata, argues that teratomata may arise either from isolated blastomeres or from fertilized polar bodies. In the latter case it is possible that during the develop-

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ment of the tumor fetal membranes may be formed. It is from the cells of these fetal membranes, according to him, that this type of tumor arises. Thus in their genesis these growths are the same as the chorio-epitheliomata of women.

Risel, on the other hand, opposes Schlagenhaufer and expresses another view. He believes that he can trace a transition between certain definite epithelial elements in these teratomata and the cells forming the chorio-epitheliomatous masses. For this reason he believes that the latter growths should be regarded as a form of embryonic epithelium arising from the epiblast and analogous in origin to the other epithelial tissues. Under such circumstances these tumors, although resembling the true chorio-epitheliomata in structure and method of distribution, are in their genesis quite distinct.

In the present case one is inclined, at first sight, to accept Schlagenhaufer's explanation rather than that of Risel. Both the gross appearance and the histological structure of the metastases, and, indeed, of the tumor of the testicle itself, are practically identical with the typical chorio-epithelioma of women; and from the fact that none of the elements of a teratoma were found in the testicular growth one might argue that the tumor was composed solely of the elements of the fetal membranes formed from the development of fertilized polar bodies included within the sexual organ.

But another explanation is also possible. If certain chorio-epitheliomatous masses embedded within a teratoma composed of all three germinal layers developed in advance of the other elements, these latter structures might come to have a subsidiary place and finally form but an insignificant part of the whole. It is thus possible that the tissue having the structure of chorio-epithelioma might entirely outgrow the other elements so that they would disappear, or be present in such small amount that without serial sections through the whole growth it would be impossible to determine their presence. This possibility, therefore, cannot be denied.

Discussion.

Dr. R. L. Lavenson: I recently had sent to me for diagnosis an interesting tumor of the testicle. It proved to be a mixed tumor

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composed of sarcomatous and carcinomatous tissue and unstriped muscle. In some areas the glandular tissue could almost be seen to be taking its origin from the sarcomatous tissue, suggesting Krompecher's claims of the interchangeability of tissues. About a year ago I obtained at autopsy a congenital mixed tumor of the kidney very much like this, in its histological elements. Dr. Scott's mention of the extensive blood metastasis in his case recalls an interesting hypernephroma of the kidney that I saw some years ago. The tumor had grown into the renal vein, and extended from the renal vein into the vena cava, and up the cava until the tip of this tail-like process rested in the right auricle of the heart.

DR. DAVID RIESMAN: There was one point in Dr. Scott's paper that interested me very much, namely, that his patient had or was believed to have had sciatica. Some years ago I saw a lad with intense sciatic pain down the leg, which had all the ear marks of an ordinary sciatica. Later, however, similar pain appeared in the other leg. A rectal examination then revealed a pelvic tumor, which at autopsy was found to be a sarcoma. Double sciatic pain, if I may refer to a clinical subject, is almost never a true sciatica, and is either due to some toxemia, like that of diabetes or Bright's disease, or is caused by the pressure of a tumor.

DR. A. J. SMITH: In connection with these metastatic malignant growths in the lung, here appearing as nodes embedded in the pulmonary tissue, I desire to report briefly another metastatic picture which was recently found in the body of a young man who died in the Philadelphia Hospital. In this case, a year or more previously, a sarcoma of the thigh had been removed by amputation of the limb by one of the surgeons, and a correct diagnosis of a group of prominent pulmonary symptoms had been made by the physician in charge, Dr. L. Napoleon Boston, who regarded the condition as due to secondary involvement of the lungs. In one of the lungs several large rounded nodes of ordinary sarcomatous appearance existed; and from one of these, penetrating the capsule of the node and the intervening pulmonary and bronchial tissues, the tumor had grown in a thick finger-like extension, about 6 or 8 cm. in length, into the lumen of the main bronchus of the lower lobe of the organ, growing downward in the penetrating direction of the tube. It completely

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blocked the bronchus, and following this complication the whole lobe was collapsed. The tube and its branches had become the seat of a widespread suppurative inflammation, analogous in appearance to the branching of an hepatic abscess due to suppurative pylephlebitis; and all along the larger branches there were developed small and medium-sized bronchiectatic pockets which added to the suppurative picture.

Another type of change met occasionally in pulmonary metastasis is peculiar enough to be mentioned here. In the extension of cancerous growths to the parietal pleura, not infrequently through adhesions or even without these by direct contact, the growth may pass to the visceral pleura, and here occasionally extends into the subpleural lymph spaces widely over the surface of the lung. Thus the organ beco nes more or less encased in a box-like sheet of the malignant tissue, much as the chest itself is often partially encased in the so-called *cancer en cuirasse.* The subpleural encasement is of course not likely to be complete, but it is apt to be sufficiently extensive to materially interfere with the pulmonary movements—respirations, and thus marked dyspnea, rapid and shallow breathing, violent cough, and pleural pain upon any especial effort at full inhalation or exhalation, come to be induced among other symptoms as prominent features of the clinical course of the case.

October 16, 1908.

Congenital Nephritis.

By HOWARD T. KARSNER, M.D.

(From the Laboratory of Pathology of the University of Pennsylvania and the Philadelphia General Hospital.)

The following case is of interest not only because of its rarity, but because of its suggestions in the realm of etiology of nephritis; for, although we all stand ready to credit nephritis to some very definite infection or to the presence in the body of some fairly well-defined irritant whose nature we have at least approximately determined, yet the occurrence of this disease in the newborn child of an apparently

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healthy woman leads one to think that the delicacy of this finely constructed gland may be susceptible to the irritation of many substances of which we have little conception at the present time. That the kidneys of young children may become diseased because of the influence of an irritant which seems to be of little or no etiological moment in adults is well borne out by reference to the literature. Acute indigestion and inflammatory conditions of the gut tract, cold plunges, exposure to high grades of heat, calcareous and hemosiderin deposits in the tubules, interstitial hemorrhage, and even icterus, in addition to the causes found in later life, such as passive congestion, ingested irritants, and infections, have all been shown to play a part in the etiology of nephritis of very early life.[13] The delicacy of the infantile kidney is well shown when so simple a condition as vaccinia may produce nephritis.[15] That uric acid infarcts may produce nephritis in very early life is well known,[10] and that such uric acid infarcts may occur before birth has also been demonstrated.[12] Parental syphilis as an etiological factor in infantile nephritis, and even in the nephritis of premature and stillborn infants, plays an important part. Here, of course, the nephritis is most usually of the interstitial type, but in some cases in which purely parenchymatous changes have occurred the cause seems to have been undoubtedly syphilis. Spiess[19] noted this in 1877, Stroebe[20] again in 1891, and Cassell[7] in 1904 made a complete study of twelve cases of undoubted hereditary syphilis, the patients dying between the fifth week and the fifth month, and of six cases the patients being syphilitic and prematurely born. Ten of the twelve patients in the first group "showed more or less severe parenchymatous alterations which exhibited an extremely wide variation in extension and intensity." Of the six cases in the second group, four patients showed severe alterations in the epithelium of the uriniferous tubules. In these cases, however, the glomeruli "showed no serious diseased process."

The case which I report is one of acute parenchymatous disease. I was unable to locate the father, but the mother's history and physical examination were negative, and the baby itself showed nothing to indicate syphilis. Baby and mother were on the service of Dr. Reynolds in the Philadelphia General Hospital. The autopsy on the baby was made during my own service in that institution. Dr.

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Reynolds and his resident, Dr. Jackson, have furnished me with the physical examination and the account of the birth, life, and death of the infant.

E. B., white, aged thirty-four years; born in Ireland; occupation, housework; unmarried; was admitted to the hospital in the early stages of labor.

Family History. Father and mother dead of unknown cause. Three brothers and two sisters are all living and well. One sister has five children, all living and well, and has suffered no miscarriages.

Previous Personal History. Patient had mumps and measles in childhood and had suffered from no serious or long-standing illness in adult life. Menstrual flow began at sixteen years and continued normally until last July. She denied having been pregnant before, and denied ever having had intercourse before the one which caused the present pregnancy. She absolutely denied venereal history of any sort, although she said she had had slight attacks of leucorrhea within the past three years. She denied using alcohol or other drugs, but is a moderate coffee and tea drinker.

History of Present Condition. Menstrual flow was last seen in July. Passed through the usual course of pregnancy with its signs, except that the breasts did not enlarge appreciably.

Physical Examination (by the resident physician, Dr. Jackson). Well-developed adult, white Irish woman of moderate stature. Eyes gray; pupils react to light and accommodation. Tongue coated and dry. Pulse: tension fair, slow, and of good volume. Head, negative. Chest, negative. Abdomen pendulous; fetal mass on the right, feet on left side. Vaginal examination: net-like processes about the orifice. Cervix soft, flattened, and admitted two fingers. Extremities, negative.

Ward Notes. April 22, 1908. Patient went into labor at 3 A.M., membranes ruptured at 8.30 A.M., child was born at 9.45 A.M., placenta at 10.15 A.M. Morphine sulphate, gr. $\frac{1}{8}$ and hyoscine hydrobromate, gr. $\frac{1}{100}$ given hypodermically about one-half hour before active labor began. Child born in left occipito-anterior position. Labor normal. Child apparently well developed, showing no abnormalities except cyanosis, which continued even after respiration had been established. A few minutes after cutting the cord the child became

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more deeply cyanotic, respiration failed, and died about forty-five minutes after birth.

April 30, 1908. Uninterrupted recovery on the part of the mother.

(NOTE.—At about the time of death of the child the resident physician attempted to inject a small dose of strychnine directly into the heart, an attempt which was without observable effect.)

The mother's urine showed a light yellow color, was clear, specific gravity 1015, contained a few epithelial cells and detritus, but no albumin, sugar, or casts.

Autopsy on the body of the child was made by me forty-eight hours after death. M. B., aged forty-five minutes. Body of a white female infant, well developed and well nourished. Fairly good growth of light hair, with the general cutaneous redness of the newborn. No apparent cyanosis. Primary incision showed nothing abnormal. On lifting the chest flap, a needle puncture was found in the fourth interspace in the midclavicular line, which could be followed down into the lower lobe of the left lung without showing any evidence of having struck the heart or pericardium.

Abdomen. Abdominal cavity showed a smooth, glistening peritoneum; normal situation of organs. Belly cavity contained approximately 100 c.c. of clear, brownish-yellow, limpid fluid. Spleen approximately of normal size; smooth, glistening capsule; cut with ease and showed a moderately firm, slightly bleeding cut surface, without distinct markings. Left adrenal large, showed postmortem congestion. Left kidney: weight, 20 grams; measured 2 x 2.2 x 2.7 cm.; was markedly lobulated; capsule stripped with ease, showing a smooth, dark brown surface, with intense congestion of stellate veins. The organ cut with ease and showed a slight bulging cut surface; cortex measured 2.5 mm.; entire kidney substance, 1 cm.; cortex showed marked congestion; little or no striping; pyramids considerably injected. Pelvis normal. Right adrenal was like its fellow. Right kidney: weight, 18 grams; measured 4.8 x 2.2 x 2.5 cm.; capsule stripped with ease, showed a grayish brown surface with injection of the veins not quite so marked as in the opposite organ; cortex measured 2 mm., cut with ease, showed a light, yellowish brown, moderately bleeding cut surface; entire kidney substance 10 mm.; cortex was light in color and showed no stripings. Pyramids moder-

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ately injected. Bladder showed a normal mucosa; contained no urine whatever. Urachus closed. Stomach contained a small amount of frothy mucus. Mucosa apparently normal. Intestines were considerably injected, particularly in the neighborhood of the Peyer's patches; they contained a large amount of dirty yellow, fecal material. Appendix was normal. Large intestine was distended with meconium. Liver was approximately normal in size; showed a smooth, glistening capsule; cut with ease, showed a slightly bulging, grayish-brown, bleeding cut surface, in which the markings were completely obscured. Gall-bladder was distended with very viscid green bile; mucosa normal. Pancreas showed no gross anatomical change. Aorta was normal. Thymus was present, apparently normal.

Thorax. Right pleura was smooth and glistening throughout. Right lung was moderately crepitant; cut surface was light red; exuded on pressure a small amount of frothy white fluid. Left pleura was like the right. Left lung was like its fellow, except for a slightly bleeding puncture extending from the outer surface well into the lower lobe. Pericardium was smooth and glistening. Cavity contained 30 c.c. of clear, straw-colored fluid. Heart was of normal size; musculature apparently normal; thickness of wall of the heart ventricles giving a ratio of about 1 to 2 (right to left); foramen ovale patulous; valve leaflets normal in appearance and orifices of normal caliber.

Anatomical Diagnosis. Congestion of lungs; puncture wound of left lung; patulous foramen ovale; acute diffuse nephritis; cloudy swelling of liver.

Sections were prepared and examined histologically from the following tissues: (1) Thymus; (2) lungs; (3) liver; (4) pancreas; (5) spleen; (6) kidneys; (7) stomach; (8) small intestine.

1. *Thymus.* The surrounding fibrous tissue was a thin layer of loosely arranged fibers, poor in cells, in several places including a few fat globules. The gland proper showed the usual lymphoid cells in the cortex, with a looser arrangement in the medulla. The corpuscles of Hassall were numerous and discrete. No epithelium encountered. Vessels showed normally thick walls, but were densely engorged with erythrocytes. Cortex did not show demonstrable erythroblasts, but showed numerous mononuclear eosinophiles.

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2. *Lungs.* Pleura present, showing as a thin, loosely arranged layer of fibrous tissue with somewhat congested capillaries. Vesicles were moderately but universally distended, in some parts much more so than in others. No evidence of true exudate was found, although in some places the vesicles were filled with a finely granular substance which took the eosin faintly, probably serum. The alveolar walls were moderately thick in the poorly expanded portion of the lung and about as thin as those of the adult lung in the well-expanded portions. The thicker alveolar walls were made up largely of engorged capillaries, a few connective-tissue cells with oval vesicular nuclei. A few lymphoid cells, plasma cells, and leukocytes were discernible, as were also the endothelial cells of the capillaries. No evidence of excess of fibrous-tissue elements could be made out. The bronchi showed slight clouding of the epithelium, with loss of outline. Nuclei were sharply outlined, vesicular, and well stained. No desquamation or exudation. The larger vessels showed a rich supply of elastica, but were of normal thickness and make-up. Congestion was general and well marked throughout the section.

3. *Liver.* Capsule present and of normal thickness and density. Perilobular portion of capsule was also normal in thickness, but shows a few lymphocytes embedded in the fibrous meshes. Portal vein was normal; hepatic artery engorged with erythrocytes; bile ducts showed normal epithelium. The parenchymal walls were poorly outlined, granular, and poorly stained. Many of them contained minute vacuoles, probably of fatty origin. The nuclei were distinctly outlined, but faintly stained and vesicular. In many instances the nuclei were completely obscured. Definite karyorrhexis and pyknosis not demonstrable. The intervening capillaries showed numerous erythrocytes. The central veins were generally filled with blood.

4. *Pancreas.* The cells of the parenchyma were of about normal size, but showed no distinctness of outline, and were somewhat granular. The nuclei were well stained, prominent, sharply outlined, and with normal chromatin arrangement. The islands of Langerhans were present in apparently normal numbers, their cells showed the same protoplasmic degeneration as noted in the parenchyma, the nuclei being normal. The interlobular interstitial tissue was present in comparatively increased amount, but showed young connective-

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tissue cells of the oval and fusiform vesicular type, in a relatively loose network of fibrillæ. The vessels were of normal size, but considerably injected throughout the section.

5. *Spleen.* Capsule and trabeculæ of normal thickness and density. The pulp showed the usual arrangement of fine stroma and small round cells, markedly admixed, however, with enormous numbers of erythrocytes, which in many cases seemed to encroach upon the follicles somewhat. The follicles otherwise were normal in size, prominent, and showed normal elements. The vessels were universally distended with blood, but normal as to the walls.

6. *Kidneys.* Capsule almost completely stripped, leaving only a few fibrillæ on the surface. The glomeruli were of a size that could be considered normal for the time of life of the patient. The number of nuclei was markedly increased, they being for the most part oval, circular, or occasionally spindle-shaped, well stained, sharply outlined, distinctly vesicular, and with a netlike arrangement of the chromatin. The capillaries showed the presence of a moderate number of erythrocytes. The capsular epithelium was normal. The capsular space was almost completely obliterated by the enlarged tufts, and showed no appreciable exudate. The epithelium of the convoluted tubules was swollen, had completely lost outline, and was distinctly granular. In many tubules the lumen was obliterated by the swelling, in others the lumen was filled with granular detritus. A few vacuoles very suggestive of fat could be made out in the basilar portions of the cells. The nuclei showed various degenerative changes, in some cases staining diffusely blue with the hematoxylin, in others showing a peripheral accumulation of chromatin. Many nuclei were obscured either partially or completely, but no fragmentation was demonstrable. The tubules of the rays and the medullary tubules showed much less protoplasmic degeneration and normal nuclei. The bloodvessels showed normal walls, but veins, arteries, and capillaries were markedly congested. The interstitial tissue showed no proliferation. In a position corresponding to the pelvic side of the sections was found a large mass of fairly dense fibrous tissue covered with transitional epithelium, the infantile pelvis.

7. *Stomach.* The mucosa was of normal thickness. The glandular epithelium showed typical goblet-cell formation, and there was finely

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granular material in the lumina, suggesting the presence of mucus. The deeper epithelial cells showed granularity, swelling, loss of outline, and small vacuoles, probably of mucus. The nuclei were normal. The interstitial tissue of the mucosa was normal, save for the infiltration of a very few round cells. Muscularis and peritoneal coats were normal. The vessels of all the coats were moderately engorged with erythrocytes.

8. *Small Intestine.* The epithelium had disappeared, probably because of postmortem digestion. The villi showed some degeneration of the outermost cells, and there was a slight round-cell infiltration. The submucosa showed at one point a large collection of lymphoid cells, which was not sharply outlined, but spread out into the surrounding tissue. The remainder of the submucosa was normal. Muscularis and peritoneal coat were normal. The vessels generally were moderately congested.

Histological Diagnosis. Normal thymus; congestion of lungs; advanced cloudy swelling of liver; interlobular fibrosis in pancreas; congestion of spleen; acute parenchymatous nephritis; mucoid degeneration of gastric mucosa; slight lymphoid infiltration of small intestine.

This history showed nothing in the mother that I can definitely blame for the nephritis in the child. The fact that she was unmarried suggested the fact that some drug might have been used to induce abortion, and my attention was particularly directed to potassium chlorate as an inducer both of abortion[12] and of nephritis, but the history revealed nothing of this.

The autopsy showed nothing at all indicative of the cause of the nephritis except the slight lymphoid infiltration in the submucosa of the small intestine, which in view of the work of Jacobi[16] and of Holt,[14] and associated as it was in this case with a parenchymatous degeneration of the liver, would suggest the possibility of some fetal intestinal disturbance as having induced the kidney condition. With the absence of any splenitis and the absence of anything in the gut to indicate definite intestinal disease, I cannot consider these conditions as having more than a suggestive significance.

The general congestion of all the viscera I believe to have been purely postnatal, since there was no vascular thickening, no evidence

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of diapedesis or hemorrhage, and no interstitial proliferation (except in the pancreas); hence it was probably of insufficient duration to have produced any inflammatory kidney condition.

Syphilis is naturally the disease to which we look as the most likely cause of the condition, but there were no cutaneous bullæ, no enlargements of the bone ends (no sections made), no interstitial overgrowth in the lung, no change in the capsule of Glisson, and no changes in the kidney that could be considered indicative of nephritis. The pancreas showed moderate interlobular overgrowth of connective tissue, a condition which can occur quite independently of syphilis and which has been so reported.[18] *

Parenchymatous disease of the kidney, as I have stated before, occurs in syphilis of the newborn and of the fetus, but such conditions are by no means diagnostic of syphilis. Cassell[7] says: "In reference to the diagnostic interpretation of these (parenchymatous) alterations in connection with syphilis, I speak in agreement with Hecker when I say that "we must not see anything pathognomonic or diagnostic of syphilis in these degenerative conditions." Hence I am led to believe the disease in this particular infant was in all probability of the type that Holt[13] speaks of as primary nephritis.

For justification of such a classification of this case I refer to Ballantyne, who, in rather general consideration of "The Pathology of Antenatal Life,"[14] says: "During fetal life the organism is subject, just as it is in later life, to the maladies which are caused by microbes and their toxins, and by poisons, mineral and vegetable; it may also be affected by diseases which, in the absence of fuller knowledge, we must call idiopathic. . . . So far therefore as our knowledge of the pathology of postnatal and antenatal life has carried us, it would seem that the same morbid causes are in action in all the periods into which the existence of the organism has been divided."

In how far the kidney condition was responsible for the death of the baby is hard to judge, when we remember the fact that this infant

* At the suggestion of Dr. Allen J. Smith, I stained two sections of liver and one each of lung and kidney by the Levaditi method for *Treponema pallida*, and examined them with utmost care with the aid of the mechanical stage. The result was negative. While this negative finding is by no means conclusive, yet it may be accepted as, in a certain sense, circumstantial evidence when combined with the other negative findings.

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was apparently a "blue baby" and had a wide open foramen ovale. Of course, during fetal life the activity of the kidney is not great, and we must consider the possibility of the changed conditions and activities of life having produced such an increased demand on the function of these diseased kidneys as to have completely disabled them. The infant's bladder was empty, but that may have been brought about by the usual urination which occurs soon after birth. It is hardly probable that a toxemia sufficient to cause death would occur in forty-five minutes, yet we must conclude from the pathological condition of the organs that the kidney insufficiency must have existed for some time, and that some more or less marked grade of toxemia must have existed prior to birth. In that case the additional toxemia attendant on the increased functions of postnatal life may have been just sufficient increment to cause death. In such cases "it may be said that the cause of death is birth."

A careful search of the literature shows a surprising meagreness of information in reference to nephritis in infants as young as this. Many standard text-books of pediatrics and pathology fail to mention that such a condition may occur. Many of the more modern authorities mention the primary nephritis of the newborn, but seem to think of it as a condition limited to postnatal life, and do not suggest the possibility of its being present at the time of birth and of its having originated in antenatal life. On the other hand, Descroizilles[9] mentioned it as early as 1883 as occurring "in the first days of existence." Cotton,[8] Baginsky,[3] and Henoch,[11] all draw attention to it, the last named in particularly forceful fashion. He says: "One sometimes meets with cases of most tender age in which nephritis has developed and has resulted disastrously without any cause for the condition having been discovered. I do not mean here the cloudy swelling of the cortex which often appears as a result of the disturbance of epithelial nutrition, but clinically recognizable pictures of inflammation." Ashby and Wright[2] make even a more positive assertion, saying that "in rare cases infants are born with acute nephritis," and refer to the case which is the third and most definite of the three cases that I have collected, *i. e.*, cases which have truly been born with nephritis.

CASE I.—This is Cahen's[5] case, reported in 1853, a case which was probably, but not certainly, nephritis. I quote from Cahen's paper:

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"Observation IV. A male infant of two days, not having reached term, weighing 1900 grams, and of 42 cm. total length, died suddenly as a result of convulsions on April 29, 1851. At the autopsy the principal organs were found to be normal. The kidneys were congested, one weighing 17 grams, and the other 14 grams. A few drops of urine found in the bladder gave a white precipitate of albumin."

CASE II.—Kast[17] described and pictured the gross appearance of a kidney in which histological section would probably have shown the changes of a nephritis subsequent to congestion. His report follows:

"Cyanotic kidney in a newborn. Body of an extremely cyanotic child which died during birth. All the organs showed intense venous congestion; multiple ecchymoses up to the size of lentils on the serous membranes. Lungs absolutely unexpanded. Kidneys showed marked fetal lobulation. On the cut section the black blue colored pyramids were sharply demarcated from the homogeneous light red cortex; the deep blue color of the pyramids was seen throughout their entire extent, and by close inspection was seen to be brought about by a recognizable tense injection of the venous channels up to the borderline."

CASE III.—Ashby's[1] case, as quoted in Carpenter's article,[6] is probably the most definite and certainly the most interesting case that I have found. Carpenter says: "Ashby records the case of an infant, aged four weeks, which became dropsical the day following its birth and remained anasarcous to the day of its death, and finally died in convulsions. The kidneys were pale and showed but little distinction between cortex and medulla. Microscopically, there were extensive epithelial and fibroid changes, and the small arteries appeared thickened. There was no evidence of syphilis, although he thought that suggestion worthy of consideration, but to him it appeared to be the 'exact type of scarlatinal nephritis.'"

I firmly believe that such cases as this of Ashby's and the one that I report, although at the present time to be classified only as primary nephritis, have most certainly been caused by some nephritic irritant the nature of which we do not know, but just as surely as there will come a day when there will be no *primary* anemias, so will a day come when the term *primary* nephritis will have become historic rather than practical.

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October 16, 1908.

Card Specimens Presented November 12, 1908.

DR. A. G. ELLIS:

Partial Aneurysm of the Apex of the Left Ventricle, with Occlusion of the Coronary Artery Supplying the Area Involved.

The heart is greatly hypertrophied, but the wall at the dilated point is only 0.5 cm. thick, being formed chiefly of the pericardium and the thickened endocardium; the muscle is very thin. Filling the shallow sac and occupying a large part of the apex of the cavity of the ventricle is a grayish-yellow, laminated, fibrinous clot at points 2.5 cm. thick. This had evidently arrested the aneurysmal dilatation. The aneurysm

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is the result of changes in the area induced by obliterative arteritis in the descending branch of the left coronary artery, which at a point 2 cm. from its origin was entirely occluded.

DR. C. B. FARR:

Specimens from a Case of Addison's Disease.

The diagnosis was based on pigmentation of the skin and mucous membranes, profound asthenia, with low blood pressure, mental apathy, and signs referable to tuberculosis of the lung and testicle. Male, aged fifty-three years.

Specimens are shown as follows: Fibroid tuberculosis of the upper lobe of the right lung; caseous tuberculosis of the left testicle and epididymis; fibrocaseous tuberculosis of both adrenals. The left adrenal is much enlarged, weighing nearly 40 grams, the right is about half as large. Microscopic examination confirmed the tuberculous character of the lesions. Tubercles were also found in the liver, spleen, and left lung. There was also an adhesive peritonitis.

Specimens from a Case of Stricture of the Urethra, with Pyelonephritis and Urethrorectal Fistula.

The diagnosis of fistula was based on the fact that there was a discharge of fluid resembling urine from the rectum after stool.

The specimens exhibited show: Suppurative pyelonephritis (bilateral); hypertrophy and contraction of the bladder; a fistula an inch and one-half long from the prostatic urethra into the rectum, with openings into the urethra and rectum not more than 0.5 cm. in diameter and showing no evidence of recent inflammation. In the body of the prostate the sinus expands into a small triangular sac, which contains no pus. The condition probably resulted from a prostatic abscess. Both specimens are from the medical service of Dr. Joseph Sailer at the Presbyterian Hospital.

DR. A. O. J. KELLY:

Carcinomatous Ulcer of the Stomach with Erosion of a Large Branch of the Gastric Artery.

The specimen is from I. C., a colored man, aged forty years, who was admitted to the German Hospital on September 23, 1908. The

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patient's chief complaints were epigastric pain, nausea, and vomiting of four months' duration. One month before admission he vomited blood, and on the day of admission he had a second severe hemorrhage. The hemorrhages recurred frequently while he was in the hospital, and on October 13 almost led to death. Operative intervention was contemplated, but death ensued suddenly from hemorrhage on October 24, 1908. At the necropsy the stomach was found moderately dilated and entirely filled with a blood clot forming a cast of the interior of the stomach. The lesser curvature toward the cardia was the seat of an irregular ulceration, about 10 cm. in its greatest diameter, with indurated edges. Toward one margin of the ulcer in its floor was a large branch of the gastric artery that had been eroded and evidently gave rise to the fatal hemorrhage. The indurated edge of the ulcer and the hyperplastic condition of the adjacent mucosa suggested a malignant transformation of an ulcer, a suggestion that was confirmed by the microscopic examination. There was considerable epithelial invasion of the musculature.

Secondary Carcinoma of the Liver in a Young Person, the Liver Weighing Twenty-one and One-half Pounds.

The specimen is from J. E., a man, aged twenty-one years, who was admitted to the German Hospital October 19, 1908. The patient's chief complaints were of five weeks' duration, and consisted of pain and distress in the abdomen, at first relieved by catharsis, later constant, and a feeling of weight and pain in the epigastrium. The liver was obviously much enlarged, its lower margin reaching below the transverse umbilical line. The patient suddenly collapsed and died October 25, 1908. At the necropsy the liver measured 38 cm. x 34 cm. x 19 cm., and weighed 10,697 grams (21½ pounds). It was studded with many grayish-white nodules of newgrowth. The primary tumor was in the tail of the pancreas, and was about 6 cm. in its greatest diameter. Microscopically the growth was an adenocarcinoma.

DR. JOHN SPEESE:

Sarcoma of the Breast.

The tumor was removed at operation by Dr. John H. Jopson. The patient was a woman, aged forty years, who gave the history of a

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growth which had been present for about three years, and which had begun to enlarge rapidly a short time before its removal. On palpation it was hard, the skin and nipple were not involved, the axillary lymph nodes did not show any change.

The pathological examination of the tumor reveals a mass about the size of a cocoanut, which presents a cut lobulated surface with reddish and whitish areas, and in places presenting a soft, mucoid material. The gross appearance suggests a cystosarcoma, and microscopic examination shows that the tumor is composed, for the most part, of spindle cells, small areas of mucoid degeneration, and dilatation of the breast ducts.

DR. HOWARD T. KARSNER:

Partial Cardiac Aneurysm and Anemic Infarct of a Solitary Kidney.

The two specimens were removed from the same patient, a man who died with the general symptoms of uremia. The aneurysm is situated in the apex of the left ventricle at which point the musculature does not attain a thickness of more than 1 mm. Marked sclerosis of the coronaries is noted, but the point of probable occlusion of one of the arteries is not found. A moderately voluminous laminated thrombus replaces the dilatation of the ventricle produced by the aneurysm. The heart is the seat of a moderate interstitial myocarditis and weighs 320 grams.

The kidney was situated upon the left side. It weighs 200 grams, measures 13.5x4.5x4.5 cm., is of normal shape, and is the seat of a moderate chronic interstitial nephritis. The anemic infarct is 2 cm. in width at its base and extends well down into the medulla of the organ. No kidney was found on the opposite side, and careful search failed to reveal the renal artery, renal vein, or ureter on the right side of the body. The bladder showed the plica ureterica which usually limits the trigonum at its upper margin, but neither a right ureteral opening nor any dimple suggesting its position was found.

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Card Specimens Presented December 10, 1908.

DR. H. B. ALLYN:

Specimen of Aneurysm of the Abdominal Aorta.

This specimen was removed from a patient, aged forty-five years, admitted to the Philadelphia Hospital with throbbing pains in the cardiac, epigastric, and lower thoracic and lumbar regions. He had had syphilis five years before admission, which had not been treated.

Below the ribs of the left side anteriorly was a tumor the size of a goose egg, with expansile pulsation, and not falling away from the aorta on the patient's assuming a knee-chest position. Rupture of the aneurysm was preceded by pain in the abdomen, shortly after which a large accumulation of fluid was found in the left lower abdominal cavity. At autopsy there were found dilatation of the arch and of the lower thoracic and upper abdominal aorta, saccular aneurysm of the abdominal aorta, and erosion of the vertebræ from the ninth thoracic to the fourth lumbar. At the diaphragm the aorta measured 19 cm. in circumference. The aneurysm extended for a distance of about four inches. Below it, the aorta measured 18 cm. The rupture probably occurred on the left side posteriorly, below the sac, and was retroperitoneal.

DR. H. T. KARSNER:

Specimens of Hyalocapsulitis of the Liver and of the Spleen.

These specimens were removed at autopsy from a case that had been treated in the dispensary of the University Hospital. The patient had been under observation for several months, and a diagnosis of atrophic cirrhosis of the liver and aneurysm of the arch of the aorta had been made. Both these conditions were found at autopsy, and in addition a chronic adhesive pericarditis about the large vessels at the base of the heart. But the most remarkable feature in some respects was the enormous increase in the thickness of the capsules of the spleen and liver associated with marked hyaline transformation. Inasmuch as the aorta showed a mesaortitis which was almost positively syphilitic, the hyalocapsulitis was probably of the same origin.

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DR. JOSEPH SAILER:

A Case of Multiple Valvular Lesions of the Heart and Multiple Serositis.

Male, aged twenty-six years. Heart disease recognized in childhood. Repeated paracentesis of the thorax and abdomen. Before death the clinical diagnosis of hypertrophy and dilatation of all the cavities of the heart, mitral obstruction and insufficiency, aortic insufficiency, tricuspid insufficiency, dilatation of the first portion of the aorta, and multiple serositis.

Autopsy showed marked thickening of the capsules of the lungs and liver, partial adhesive pericarditis, chronic endocarditis, tricuspid and mitral stenosis and insufficiency. There was vegetative endocarditis of the pulmonary, mitral, and aortic valves.

Aortic Valvulitis and Aneurysm of the Ascending Aorta Rupturing into the Descending Cava.

Negress, aged fifty years. Enlarged heart. Physical signs of aortic insufficiency, pulsation of the liver, an area of dulness over the upper portion of the sternum. No edema. No distention or positive pulse in the veins of the neck or arms.

Clinical diagnosis of aortic insufficiency, aneurysm of the ascending portion of the aorta.

Autopsy. Heart found to be enlarged. Aortic leaflets retracted. Large saccular aneurysm of the first portion opening into the descending cava about a whole half inch in diameter. This was evidently of long standing, because the walls were smooth. This rupture without the edema of the upper extremities has not hitherto been described.

DR. CLIFFORD B. FARR:

Specimens of Cardiac Abnormalities from the Medical Service of Dr. Joseph Sailer at the Presbyterian Hospital.

CASE I.—*Clinical diagnosis:* Acute streptococcic endocarditis, chronic endocarditis, and insufficiency of the mitral and aortic valve. The specimen shows hypertrophy and moderate dilatation of the left ventricle; recent pink, warty vegetations on the mural endocardium of the left auricle, the free edge of the anterior leaflet of the mitral

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valve, the lower surface of the anterior aortic cusp, and the adjacent endocardium; infarct of the spleen, partly broken down, occupying more than three-fourths of the entire bulk of the organ, the poles alone being free; and small infarcts of the kidneys.

CASE II.—*Clinical diagnosis:* Hypertrophy and dilatation of the heart; insufficiency of the aortic, mitral, pulmonary, and tricuspid valves. The specimen shows great hypertrophy of the right ventricle and slight hypertrophy of the left ventricle; relative incompetency of the aortic valve, without dilatation of the aorta; an elongated sac in the wall of the right ventricle, lined with fibrinous clots, communicating with the aorta just above the aortic valve, and with the right ventricle below the pulmonary valve; white, button-like elevations, 5 to 6 mm. in diameter, about one inch below the pulmonary valve; a similar, but larger elevation on the posterior and left cusps of the pulmonary valve; and a saccular aneurysm the size of a small marble, at the beginning of the descending aorta. The liver presented the appearance of syphilitic cirrhosis. Microscopic examination of the nodules in the right auricle and on the pulmonary valve supported, but did not actually establish, their syphilitic character.

Specimens of Hypernephroma.

DR. L. J. HAMMOND (by invitation):

This specimen was removed from a woman, aged forty-two years, who had known of its existence for two years. During this period there had been continuous and increasing loss in flesh and strength, so that she presented the general classic appearance of a woman suffering with malignant disease. At the operation for the removal of this neoplasm, the kidney was found anchored in a mass of inflammatory adhesions, which had almost surely existed since the time of a fibroid operation, twenty-two years before. There was a stenosis of the ureter, caused by cicatricial tissue at its lower end. The circumference of the ureter was an inch and one-quarter. It was hard and firm, and the color of an ordinary clay pipestem. The stenosis of the ureter may have played some part in the etiology of the growth. The growth itself is encapsulated, except at its inner portion, where it is adherent to the peritoneum, and to the intestines. As the result of this rupture of the enveloping capsule, there is a cauliflower-

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appearing mass, the larger of the two unequal masses representing the newgrowth.

DR. JOHN FUNKE:

Recently I removed at autopsy, in the Philadelphia Hospital, a hypernephroma from a patient in whose history nothing indicated the presence of such a growth. The patient died as the result of chronic caseous tuberculosis, tuberculosis of the peribronchial lymph nodes, tuberculous caries of the spine, and miliary tuberculosis of the lungs. The tumor is in the left kidney, one small nodule being in the cortex at the midpole, and the other just above the pelvis. There was another small nodule in the right adrenal, which was removed entire for examination.

The other specimen is from a patient who had died as the result of acute follicular enteritis and fatty degeneration of the heart. This tumor is in the right kidney. In the left adrenal was another small nodule. The larger nodule of the kidney presented an appearance like that of caseation, but microscopic examination showed merely an infiltration of lymphoid cells without caseation. There was no metastasis, and no evidence of the existence of the tumor during life. In neither case was the tumor the cause of death.

DR. E. B. KRUMBHAAR:

These two specimens are from two cases at the Pennsylvania Hospital. The first was obtained at autopsy two years ago from a patient dying of carcinoma of the gall-bladder. The patient showed no symptoms during life, referable to the kidney. Its gross appearance resembles that of the first specimen shown by Dr. Funke.

The other specimen of the right kidney was removed a few months ago by Dr. Gibbon. The patient had blood in the urine, and after both ureters were catheterized, the right secreted 9 c.c. of bloody urine in two hours and the other 100 c.c. of clear urine. The colon bacillus was isolated from the right side. The kidney was removed and the tumor was found to be a large hypernephroma. There were no other metastases, and the patient is recovering and is about to leave the hospital. The kidney, which is stretched around the tumor, shows numerous small, yellowish areas, which microscopically were

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found to be multiple abscesses. In the kidney capsule there is a thickened hard, white mass which proved to be a fibrosarcoma. These specimens are interesting as showing apparently benign forms of hypernephroma, both of which occurred with tumors elsewhere in the body.

DR. ALLEN J. SMITH:

I have brought several examples of hypernephromata from the collection of the University of Pennsylvania. The first, illustrative of the size that this type of tumor may obtain (half of a uniform enlargement of the kidney diffusely involved by the growth, weighing over five pounds and one-half, and measuring over 32.5 cm. from pole to pole, about 14 cm. from the position of the pelvis to the lower convex surface, and 10 cm. in thickness), was presented to the collection by Dr. Park Willis, a surgeon of Seattle. It was obtained by him from the body of a white woman. The tumor had been recognized for more than a year prior to her death. She refused operation, and died in 1906.

The second specimen was removed at autopsy from a man who died in the Germantown Hospital in 1906, and was obtained through the kindness of Dr. Burton Chance. The patient was a white man, aged forty-three years, from whom, in 1905, Dr. Chance had removed a metastatic hypernephroma of the left iris. Later, the eye was enucleated at the Philadelphia Hospital by Dr. Croskey. In April of 1906, an operation by Dr. Stewart for intestinal obstruction showed an intussusception of the lower part of the ileum, an intra-intestinal tumor about the size of a walnut forming the apex of the intussuscepted part. Three polypoid subserous tumors, one in the ileum and two in the colon, were seen, but not disturbed. The intussusception was reduced, and the abdominal wound closed. About a month later, intestinal obstruction again ensued, and the man died. At the autopsy the primary growth was obtained. It is a sharply circumscribed, spheroidal node, about 3 cm. in diameter, projecting from the upper lobe of the kidney. A second smaller nodule is seen in the renal parenchyma, between the first and the pelvis. Only one of the subserous tumors noted at Dr. Stewart's operation was found, one of those on the colon, the other two having completely disappeared; and

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the remaining one being in a softened and hemorrhagic condition. This specimen shows double intussusception of the ileum, each with a secondary hypernephroma at the apex, as the cause of the intestinal obstruction. There are perhaps two dozen other polypoid hypernephromata projecting into the lumen of the gut at various positions, ranging from small size to a diameter of 4 or 5 cm. Secondary involvement of the peritoneal lymph glands and nodules in the retroperitoneal cellular tissues were encountered. No metastatic tumors existed in the lungs. The spontaneous disappearance of some of the metastatic formations in this case may be due to an absorption following necrosis, or perhaps to autolysis, similar to that often met with in the medulla of the adrenal after death.

The third specimen is one whose history is unknown to me. It is a lung, with a number of nodules the largest being about 5 cm. in diameter, which show under the microscope the typical structure of hypernephroma; and are from their number, round shape, and definite encapsulation, considered to be secondary growths from a tumor, presumably in the kidney. In passing, it may be said that the lung is one of the most common sites for the metastatic formation of these tumors; and the intestinal wall, the subcutaneous tissues, and especially the eye (exemplified in the second case presented) are rarely known to be thus invaded.

The Transmission of Disease by Insects.[1]

By F. CREIGHTON WELLMAN, M.D.

I WISH to bring before you a few observations that I have personally made, which are illustrative of the principles that should guide us in the study of this subject. Sir Lauder Brunton once made the statement that the study of tropical disease had largely confined itself to an investigation of the insects that carry disease, and I have heard Sir Patrick Manson say that no one is competent to make studies in tropical medicine until he is first a naturalist. One of the

[1] By invitation.

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disgraces of the medical profession is the inaccuracy with which the arthropods which carry disease are described. I should like to throw out the suggestion that young aspirants in the field of tropical medicine should do a moderate amount of systematic zoölogical work. It seems to me that a body of men of such scientific standing as our own profession should try to do something to remedy this defect, and that those who are interested in medical education should insist upon that accuracy of statement which is necessary in investigating the carrying of disease through arthropods. In making card catalogues of the literature of the subject I have found numbers of papers containing valuable facts, but which are practically valueless on account of the impossibility of discovering the particular genus, species, or order of insects that forms the basis of the investigation.

I shall begin my discussion by considering one genus of ticks, as illustrative of the work that remains to be done on that subject. This is *Ornithodoros*, of which there are two species in Africa (*O. moubata* and *O. savignyi*). These species were originally confused, but on careful study they were found to be distinct species. In following up the morphological features of the tick, we found that one of these forms (*Ornithodoros moubata*) carries certain diseases, the other not being a competent host. This genus is widely distributed in Africa and Asia, and there are even four species of it found in America. The African disease-carrying species is the bearer of two diseases, one of which is the African relapsing fever, tick fever, or spirochetosis, first described by Livingstone, the explorer. The organism involved (*Spirochæta duttoni*, named after Dr. Dutton) is morphologically distinct from *Spirochæta obermeieri*. The former organism is carried by *Ornithodoros moubata*. The disease produced by this organism, relapsing fever, is very important economically; for in Africa, where large numbers of men are required for building railroads, this disease has caused the companies to lose a great deal of money by laying up a large proportion of the men. Half the force are sometimes sick with exacerbations of this fever. On investigation, I found that the ravages of the disease could be checked by having the men sleep in hammocks suspended by ropes. It was the knowledge of the character and habits of the insect that enabled us to protect the patients.

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Another interesting discovery that I have made is that the tick also carries a filaria. I was loath to accept my own findings in regard to this matter. I worked about two years on it, and prepared a preliminary report and sent it to Mr. Low. After it had left my hands I feared that the discovery was too good to be true, and telegraphed Low to hold the report. After further observation, however, I came to the conclusion that there could be no doubt of the fact. I also studied methods of inhibiting it, and found a hemipterous insect (*Phonergates bicoloripes*) that preys exclusively upon this tick. A large number of these insects were found where the ticks were most common. This insect grasps the tick, sucks it dry, and throws the exuviæ away. This fact opens up ground for speculation; because, like the so-called kissing-bugs in the United States, this insect is known to bite human beings, and might transmit to them the disease with which it had become infected by eating this tick.

I found also a fungus that is killing these ticks, a fungus similar to that known as *Empusa muscæ*, which is found in this country on flies pasted to window panes. Neither of these methods of exterminating the tick, however, is of practical importance. This genus of ticks should be investigated. I believe that the tick fever of Persia will also prove to be a spirochetosis. The geographical distribution of these parasites coincides with the distribution of this genus of ticks. I should like to see a careful investigation into this subject. I could not carry one out, as, on account of ill-health, I was compelled to return to Europe.

I shall next consider the myriapods. These insects in Africa are sometimes venomous (*Scolopendra*, *Cormocephalus*, etc.). I found that a *Julid* centipede, which is incapable of biting, at the end of the dry season, when the struggle for existence becomes hard, excretes from the *foramina repugnatoria* a substance that runs down its legs and makes it venomous. Nothing, however, has been learned to incriminate them as carriers of disease; but they are decidedly worth studying farther.

Of the Hemiptera, the bedbug (*Cimex*) offers a most fruitful field for research. Captain Patton writes me that the species once disseminated throughout India (*Cimex rotundatus*) no longer exists except in one or two localities, *two species* new to science having

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taken their place. In West Africa the forms of bedbugs supposed to be there are absent, and a *new form* is the kind most common on the coast. There are a number of Reduviidæ bugs that bite, and inject into the system a poison giving rise to serious symptoms.

I shall now consider the Orthoptera. It would almost seem ridiculous to imagine that these could be responsible for the transmission of disease, but I regard it as eminently possible. There is an *Orthopteron* (*Hemimerus talpoides*) that has been found to be parasitic on mammals. It is parasitic on the yellow rat of West Africa (*Cricetomys gambianus*); and it is quite possible that it may be of pathological importance—not necessarily as a parasite, but as an intermediate host. I have found a *giant earwig* (*Dacnodes wellmani*), an inch and a quarter long, which is able to draw a drop of blood. It lives in refuse and has an evil reputation, being nearly always infected. I found that this is not a unique case, a species in Australia (*Anisolabis colossea*) having the same unpleasant tendency to bite, and being feared by the natives in the same way. So we see new vistas opened up, and the field is almost limitless.

The next heading is the Diptera, in which are included mosquitoes and flies. I am not going to weary you with a prolonged discussion of the mosquito, but I should like to say that I have found in West Africa that 23 per cent. of one species of mosquito (*Myzomyia funesta*) taken at random were infected. Another species of mosquito which I discovered in Africa (*Pyretophorus austeni*) must be taken into account, about 3 or 4 per cent. of these being infected. Before leaving the subject of mosquitoes, I would say that filariasis is closely connected with these insects also, *Mansonia uniformis* in the district studied by me serving as an intermediate host for *Filaria bancrofti*, and other species occasionally doing the same. You are doubtless familiar with Manson's theory regarding the origin of elephantiasis, with which I personally disagree. His belief is that the adult forms of the filaria are injected into the human system and go into the lymphatics. If the female happens to be near the surface and to be injured, not sufficiently to prevent her producing eggs, but sufficiently to prevent their being properly developed, these eggs block up the lymphatics and produce elephantiasis. Unfortunately for this theory, I found that in the district in which this disease is most common large numbers of

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natives subjected to a blood examination at night had no filaria present. The large series of cases examined proved that where elephantiasis is most common, filariasis is not very prevalent. I found a large district in which several hundreds of patients examined at night failed to show one infection with *Filaria nocturna;* and elephantiasis was more common in that place than in any other district visited by me, with one exception. Whatever may be the predisposing cause of *elephantiasis arabum*, a great factor in its production is, I am inclined to think, secondary streptococcic infection. Its lymphoid importance can be explained on that hypothesis; and I believe that our conception of the etiology of the disease will have to be changed. While I am on the subject of African Culicidæ, I may mention that there has been a new genus and subfamily of mosquitoes described, the description being founded upon female specimens, which had a seventh scale wing. In breeding from these, however, I found that the males did not share this peculiarity. Until research can be conducted on sounder basis, the study of mosquitoes will present considerable difficulty.

In the order of Diptera there are also a number of biting flies. One local species, *Simulium wellmani*, is an awful pest. It may not carry disease, but it certainly produces severe exacerbations of fever. In speaking of this species of fly, I should not like to say that it is not of pathological importance. In one genus of the Ephydrid diptera, part of the insects are in their larval stages distinctly aquatic, and others live on the stalks of plants. One would not think that such a fly would be parasitic; but one day I saw a fly closely related to the one that lives on the stalks of plants parasitizing on some ants, and collected some specimens. This shows that one cannot tell what may be the importance of apparently harmless flies that one has overlooked. A genus not supposed to be of pathological importance has been proved to carry trypanosomiasis. In West Africa I discovered three or four flies (*Anthomyia*, *Sarcophaga*, etc.) that had never before been convicted of myiasis. There is one fly (*Auchmeromyia luteola*) that, in its larval stage, has the very unpleasant habit of sucking blood like ordinary vermin; and it may transmit bacterial infection. Another fly (*Cordylobia anthropophaga*) common in West Africa has larvæ that invade the skin and produce carbuncles and

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boils, and it may be of more pathological importance than lies upon the surface.

The tsetse flies are the most important groups of the Diptera in West Africa. Manson has wisely said that he thought that the initial step in the investigation of this disease should be to send out trained zoölogists, men familiar with the habits and the bionomics of insects, to study on the ground the biology of these flies, thus preparing the way for the thorough work of the pathologist. In one district alone thirty thousand persons died in one year of sleeping sickness. Fortunately, this disease is confined to Africa and a small part of Arabia. It is, however, a disease easily dealt with from the preventive standpoint. The tsetse flies live in belts; and if one is ten feet, one might almost say, outside of a fly belt, one will not be bitten. As illustrative of this fact, I will relate the following circumstance: There was a fly belt in a certain city. Large native caravans, in going into the interior, used to cross the river in the midst of this belt. The result was that cases of sleeping-sickness were brought down to the coast. The disease thus introduced decimated whole districts. I made an investigation of the matter, as the consequence of which I recommended that the road be resurveyed so as to cross the river a few hundred yards farther up stream; and no new cases were afterward found originating from that locality. One village situated in a fly belt was also decimated, and I recommended that its location be changed. This was done, and the village was rebuilt less than a quarter of a mile away from its original site. The man that owned the village could not, however, induce his native boys to go there, because they were afraid of the disease; but I took some of my boys there, and to this day there has not been a single case of sleeping sickness in that village. A man who subsequently bought some of the land on which the village had been situated insisted upon placing some of his bungalows in one corner of the belt. I tried to persuade him not to do so, and gave my reasons; but he thought that I was mistaken, and refused to be guided by my counsel. This man is now in London, suffering with the sleeping sickness, and his plantation is in ruins.

These fly belts change in location from time to time, probably because the fly deposits its pupa directly, and must do so in sufficient

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humidity and warmth to allow its young to develop. Another relation of the tsetse fly is with cattle. A new subspecies of this fly, *Glossina palpalis wellmani*, has recently turned up. I hope to hear that the commission to study sleeping sickness recently appointed may bring forth fruitful results, and that this disease may soon become a thing of the past.

The next order of the Insecta to be considered is the Coleoptera, or the beetles. It may be unusual to think of beetles as causes of human disease and suffering; but I found the larva of a beetle (*Drilus sp.*) with brittle spines on it. When one steps on this with bare feet, it produces serious results. Another species of beetle sometimes causes sloughing from stepping on its larvæ. In British Guiana Mr. Daniels found coleopterous larvæ in an abscess in a human being. There are beetles (*Platypsylla castoris*) that live parasitically on animals, just as a louse lives on a person. We should not, therefore, be too dogmatic regarding this matter. Beetles deserve further study, and something may be found to incriminate them.

Another order of the Insecta is the Lepidoptera. Among the caterpillars I also found some that cause disagreeable symptoms. There are parasitic Lepidoptera. One species is parasitic on the South American sloth. A careful study of the habits of these insects may bring to light something novel.

The last order of insects to be considered is the Hymenoptera. I have found only one species of this order supposed to be of pathological importance. This is a species of the genus *Mutilla*. Anthrax is very common in the Island of Cyprus. On a native of that island ill with this disease an insect called σπαλαγγι was found. Upon investigation, large numbers of these insects were found upon the bodies of sheep dead with anthrax. Children are fond of playing with these insects, and it is believed that they are responsible for the dissemination of anthrax in Cyprus.

In closing, I wish to lay stress upon the third factor in tropical diseases, the first two being the patient and the arthropod that confers upon him the disease. The third factor is constituted by the dark-skinned race, who act as a culture medium, carrying the infective organisms without visible harm to themselves, but transmitting them to the white men.

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This is the case with malaria in Africa. It is the custom for the planter to have the native boys near his quarters, and their blood is teeming with malarial parasites. I made about one thousand examinations for malarial parasites, and found that at six months the children of the negro race began to have enlarged spleens, which had considerably lessened in size by the age of two years, and at the age of twenty were almost or quite normal. It is a case of racial immunity. The parasites circulate in the blood, especially that of the children, and the white men die through association with them. The third factor, therefore, is the dark-skinned race, who place on the white man an enormous handicap. Preventive medicine must consider this factor; and I believe that along these lines there are opportunities for research that will yield rich results.

Discussion.

Dr. Henry Skinner: The importance of this subject is very great, and it is well to remember that the advances are being made along the line of prevention of disease and especially by the medical biologist or the medical man who has zoölogical and biological training. One of the first observations—in fact, the first observation in the world—on the transmission of disease by houseflies was made by a distinguished Philadelphia naturalist and anatomist, Dr. Joseph Leidy (Professor of Anatomy at the University of Pennsylvania), just after the Civil War. He discovered that hospital gangrene was transmitted almost entirely by means of houseflies.

It is along the line of prevention that the question of the control of malaria and of yellow fever has been absolutely solved for all time, because we now know how to prevent the transmission of these diseases. The whole question is simply one of economy and of engineering, and this is largely true of all other insect-borne diseases. The mortality from typhoid fever is very great in camp life. During the British-Boer War the meat hung up in camp could not be seen for houseflies, and much of the great mortality from typhoid fever during that war—a mortality many times greater than that due to battle—can probably be traced to this fact. To give another illustration of the

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great danger from typhoid fever in camp life, I may mention that during the French expedition to Madagascar only 29 persons were killed in battle, while 7000 died of tropical diseases. In the Spanish-American War, the First Regiment, N. G. P., had 69 cases of typhoid fever, with 12 deaths. The men had to walk through excrement to get to the latrines. These and other causes of typhoid fever in camp life might have been prevented. I think, however, that if we depend upon inoculation or vaccination as a means of preventing the spread of typhoid fever, we shall make a great mistake.

One very interesting fact regarding the species of fly mentioned by Dr. Wellman (the tsetse fly) is that it deposits a full-grown, living larva, which goes into the ground and changes into a pupa, soon becoming adult. We do not know, however, that the life histories of other species of fly are parallel with this; and it is possible that we may be able to discover a point in the life-history at which flies are vulnerable and can be destroyed. The common housefly deposits its eggs in horse manure; but other species of fly of the same genus deposit a full-grown larva, just as is the case with this *Glossina morsitans*. It was through a study of insects that yellow fever and malaria were overcome.

We can all appreciate the work that is being done by men such as Dr. Wellman. I simply wanted to emphasize the point that the men who work in this field should have the same kind of training he has had, very broad and general. They should have biological training, and should not look too much to the medical end of the work.

December 10, 1908.

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Peculiar Blastomycetoid Organisms Met in Two Cases of Parasitic Conjunctivitis.

By W. C. POSEY, M.D., J. T. CARPENTER, M.D.,
C. M. HOSMER, M.D.,
AND
ALLEN J. SMITH, M.D.

(From the Pathological Laboratory and the Ophthalmic Department of the Pathological Laboratory of the University of Pennsylvania, Philadelphia.)

THE agents of infection in the cases reported from time to time as due to the group of organisms loosely spoken of as blastomycetes are clearly divisible into several types; and there are reasons for believing that with advance of our knowledge it will be found that greater differentiation will be accepted than is now even tentatively considered. In a number of the cases on record the organisms were found only after histological preparations had been completed and examined and when no longer opportunity obtained for culture study. In other cases efforts to cultivate the organisms have for one or other reason failed. So that, all told, the list of instances in which both histological recognition and satisfying culture observations are recorded is by no means a wide one, and surely does not exhaust all the types of microörganisms which may constantly or in some special phase of their existence present a blastomycetoid appearance. Among the earlier accounts of such infection it is well known that the writers, as Wernicke[1] (*coccidium*) and Rixford and Gilchrist[2] (*coccidioides*), regarded the organisms as protozoan in character; although in the light of cultural studies in subsequent cases from Moffitt and Ophüls[3] to the present, there can be no doubt that these earlier cases are to be properly included in the general blastomycetic group. Whether, however, all of the instances in which failure to cultivate a definite vegetable organism must necessarily, because of histological analogies, also be referred to the same class, is open, perhaps, to at least a shadow

[1] Centralbl. f. Bakteriol. u. Parasitenk., 1892, vol. xii, p. 959.

[2] Johns Hopkins Hospital Report, 1896, vol. i, p. 209.

[3] Philadelphia Medical Journal, June, 1900; Journal of Experimental Medicine, vol. vi, p. 443.

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of doubt; and it cannot be held *a priori* that the possibility of protozoan infection can be entirely set aside and that no confusion can take place. Moreover, it is clear from any careful study of the undoubted vegetable organisms in the various cases[1] that at least three morphological types have been encountered, including (*a*) non-mycelial organisms (blastomycetes), (*b*) oidium-like fungi, and (*c*) more definite moulds of the group of the hyphomycetes. It is to be remembered that even the organisms which culturally show the most marked tendency to mycelial development do not at all, or only in the most restricted degree, exhibit this feature in their occurrence in lesions produced by them; that in other words they revert to a blastomycetoid phase, or that their ordinary vegetative mode of existence is suppressed for a definitely monocellular reproductive mode (by budding). Nor do we possess any idea as to the limit of such modifications by the submergence of this or that type of true fungus in the animal tissues, or whether, in fact, similar appearances might not be assumed under like circumstances by allied groups, as the myxomycetes. Nothing but continued observation and record, correlated with experimental inoculations, can finally set the limits to such speculations and definitely fix the lines of reasonably easy identification of the bodies as they are encountered in the tissues in the various lesions in which they may from time to time be met.

It is with the double purpose of placing upon record the observation of such bodies in two cases of conjunctivitis in human beings, and of presenting certain unusual characters of the organisms encountered, that this paper has been prepared. It is most unfortunate that in each case, because of the absence of any suspicion on the part of the clinicians that such organisms were present in the lesions and because of the prompt healing of the slight operative wounds and their complete non-recurrence, no cultural studies were carried out. The presentation of the paper has been delayed for some months in vain, in hope that either in private practice or in the dispensaries open to our studies further material might be encountered from which cultures could be obtained. In each case the small nodular conjunctival growth was immediately placed in fixing solu-

[1] V. Ricketts, Jour. of Med. Research, December, 1901, vol. vi, o. s., p. 373.

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tion upon removal, and only after routine preparation of sections were the organisms observed in the laboratory. Nevertheless, there are such striking differences evident in the bodies encountered, in comparison with any of those which have been thus far recorded within our knowledge, that, in spite of lack of any information of what attempts to cultivate might have shown, there can be practically no doubt that these cases mark a very decided widening of the field thus far appreciated for blastomycetoid parasites of man.

The first case appeared in the practice of Dr. John T. Carpenter. The patient, a young white Philadelphia lad, aged twelve years, in excellent general health, had about a month before he applied for treatment injured an eye by falling upon a stick which abraded the conjunctiva more or less. When he was seen by Dr. Carpenter there existed a papillomatous growth of several millimeters' diameter, slightly tongue-shaped, with rounded surface, soft and only moderately red, in the lower inner conjunctival cul-de-sac. Aside from this there was present nothing more than a slight general catarrhal conjunctivitis. The growth was at once removed by the physician, placed in a formalin solution, and some days later was sent into the Ophthalmic Department of this laboratory, where it was sectioned and examined by Dr. Hosmer, who found the bodies. The wound occasioned by its ablation quickly and thoroughly healed, and there was no recurrence. At no time was there evidence of any systemic disturbance.

The second case occurred in the practice of Dr. W. C. Posey only a few days after the first (both in the winter of 1906–1907), presenting much the same history—but no connection whatever existed between the individuals affected. This second patient, also a young white boy, aged about fifteen years, residing in the suburbs of Philadelphia, had sustained a slight ocular injury about three or four weeks previously by being struck in the eye by a tennis ball during his play. A general monocular conjunctivitis resulted, at first of some severity and attended by more or less conjunctival edema. When first seen by Dr. Posey this had largely subsided, the conjunctiva generally being practically normal, the swelling which had been present having quite disappeared. There had appeared, however, about ten to fourteen days after the acute symptoms had subsided, a small poly-

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poid growth about 3 mm. in diameter, with a short stout pedicle, soft and of a light red color, growing from the tarsal conjunctiva of the upper lid, about 4 or 5 mm. from the ciliary margin. The growth, which was solitary, had a smooth surface. It was excised without difficulty; the excision occasioning but little hemorrhage. Healing was prompt and there was no recurrence. There was no glandular enlargement at any time, and no indication of the least systemic disturbance. In this case, as in the first, the apparently trivial character of the lesions and the practical disappearance of the primary acute conjunctivitis occasioned the neglect to make any sort of bacteriological examination prior to the removal of the nodules; and again the tiny growth was merely placed in formaldehyde solution and sent shortly after to the laboratory for histological examination, where in due course the parasitic bodies were found and their practical identity with those of Dr. Carpenter's case at once recognized.

Since these cases, a number of apparently similar conjunctival nodules have been examined, obtained from different ophthalmic surgeons of the city; and numerous microscopic examinations of, as well as culture attempts with, the conjunctival secretions of cases of conjunctivitis have been made, with the hope of meeting similar parasitic bodies in a living state which might be used in studying their biological characters—thus far without success.

The histological features of the two polypoid growths are practically identical and the appearances of the parasitic bodies in the two indistinguishable so far as comparisons can be made at present. For this reason the following description of Dr. Posey's specimen[1] is alone given in detail, with suitable reference from time to time to Dr. Carpenter's.[2]

The epithelial surface of the nodule is unbroken, but in several places is considerably thicker than normal, the excess projecting more deeply into the subepithelial tissues. At places there is marked leukocytic infiltration of the layer. No mitoses have been found in the epithelial nuclei, but occasional hyperchromatosis and excess in size of the nuclei are further evidence that proliferative changes

[1] University of Pennsylvania Pathological Histology, No. 1334.
[2] Ibid., No. 1334, *a*

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are proceeding in the tunic. On the other hand, occasional cells are found which are more or less vacuolated from cellular edema; and here and there are mucoid cells, their mucinous contents staining blue with the hematoxylin dye. The subepithelial tissue of the polyp is composed of a connective tissue loose from edema, containing a fair number of capillaries and small arterioles and venules, and the seat of a rich but irregular cellular infiltrate. No portion of the tarsal plate tissue is included in the sections, the growth being strictly limited to the conjunctiva. At least one small seromucinous gland is caught in the serial sections, showing in its duct and small acini numerous leukocytes. The polypoid growth is evidently largely the result of a localized edema, together with a polynuclear leukocytic exudate, the presence of a large proportion of the lymphocytic type of plasma cells and some proliferation and swelling of the fixed connective-tissue cells and of the endothelium of the lymph spaces. About some of the bodies to be described special leukocytic accumulation has taken place to the formation of miliary abscesses. There are no giant cells to be found in any of the sections in either case; and in neither case was there more than a rare discovery of eosinophilic cells or of mast cells. All through this altered subepithelial tissue (but in no section in the epithelial layer) lie special parasitic bodies. For the most part these are spherical or spheroidal, many, however, presenting in section (Fig. 1, *a*) a crescentic outline (interpreted as spheres having one side collapsed or pressed inwardly, like the cup resulting from compression of a rubber ball). They vary in size to a marked degree, the smallest noted measuring 0.017 mm. in diameter (Fig. 1, *b*), the largest, 0.33 mm. (Fig. 1, *f*). These largest examples are all filled with sporoblasts; the largest ones not exhibiting such features (as the one in Fig. 1 between the reference lines, *a* and *d;* or the two well-focussed and more highly magnified bodies in Fig. 3, or the four near the four margins of Fig. 2) having diameters of 60 to 80 or 90 mm. They are provided with a sharply defined, double contoured wall, smooth and unmarked, and, except sometimes at one place to be further mentioned hereafter, of uniform thickness throughout the circumference (ranging up to 4 mm. in the best-developed examples). In well-developed parasites this wall takes a light pink color when a hematoxylin and eosin stain is employed,

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but is metachromatic with thionin; even with iron-hematoxylin alone also assumes a pink to red color. The contents of these bodies vary with the development, which is apparently not entirely a matter

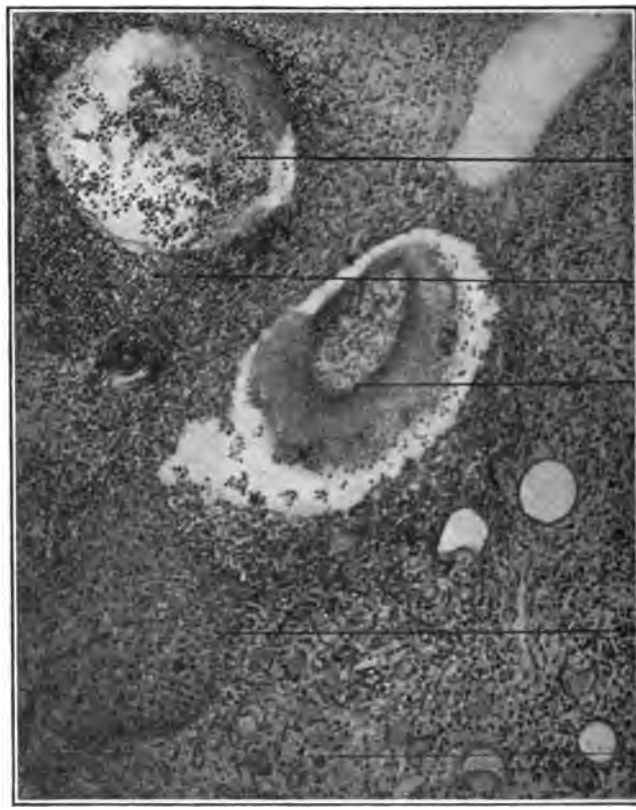

FIG. 1 (from Case II).—*a*, cup-shaped organism; *b*, one of the smallest intermediate forms; *c*, an area of epithelial cells extending more deeply than usual into the general tissue of the growth; *d*, large mature and ruptured body with wall everted, the convex side of the wall being really the inner, and the mass of cells enclosed in a cyst-like space being leukocytes gathered together by the recurved wall; *e*, a zone of leukocytes surrounding a large body filled with sporoblasts; *f*, scattered throughout the tissue are numerous parasites of various sizes, some spherical and others cup-shaped.

of size, although the larger forms are always well developed). In a number (which are not necessarily of the smallest size) the substance is of a plasmatic appearance, staining a light blue with both

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hematoxylin and eosin and also with thionin and with methylene blue; a fine reticulum with a faint pink to purple tint being distrib-

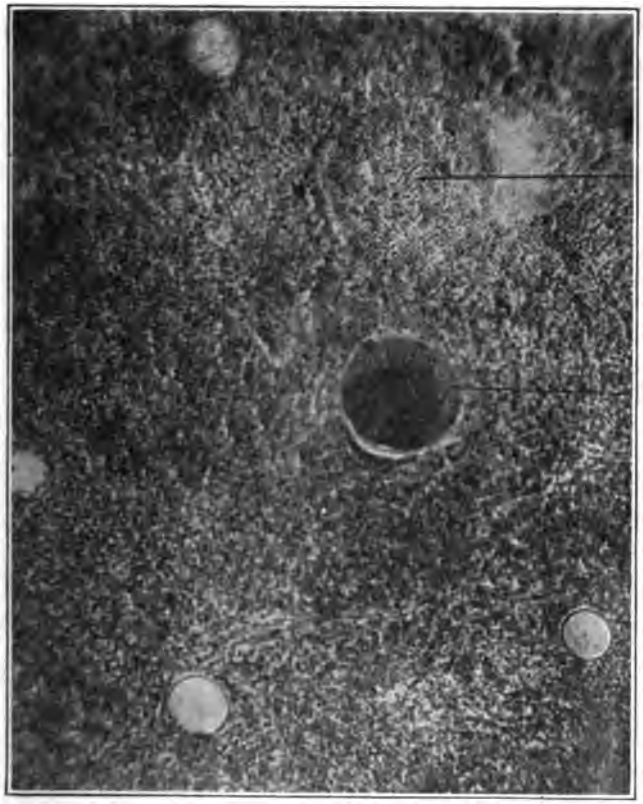

FIG. 2 (from Case I).—Photomicrograph made at a somewhat lower amplification than in case of Fig. 1 (the large body, *a*, is of practically the same size as *f*, in Fig. 1). The tissue generally is more densely infiltrated with leukocytes than in Fig. 1; *a*, large body filled with sporoblasts, its wall largely destroyed; *b*, a somewhat smaller body filled with spherules which are as yet not developed into definite sporoblasts. Along the four margins of the picture are four bodies of smaller size in which the contents are as yet not divided, the lower right-hand example showing the nucleus and reticulum faintly (these present in all, but not well shown because the others are not quite in focus).

uted through the material. In most of these early stages the substance fills the cell quite to the wall, which in such examples is always of the thinnest formation; and here lacks the definite double contour

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and is merely linear in section. In such examples there is apparently no definite nucleus. These the writers regard as *young forms* of the parasites in their developed phase of life. In the better developed but undivided bodies (constituting the bulk of those seen and in-

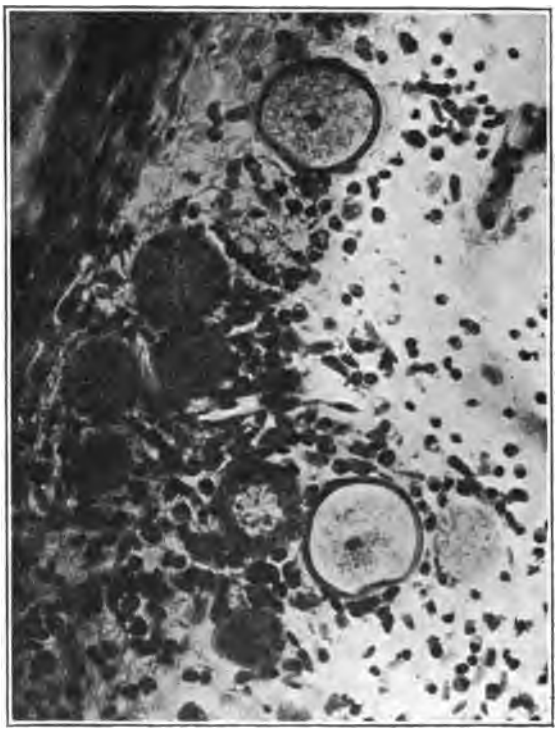

FIG. 3.—Higher amplification of intermediate stage of organisms. Two bodies are clearly in focus, showing the double-contoured wall, the peculiar flattening suggesting a micropyle, the nucleus, and the reticulum. With a hand lens used upon the photograph the chromatin granules scattered upon this reticulum are easily seen, but are not as well made out in this reproduction. To the side are a number of the earlier stages, all somewhat out of focus, but clearly showing the fact that the wall is not fully formed, and showing no clear nucleus.

cluding some of the smallest measurement, and regarded as *intermediate stages* of the developed phase) there is a small well-defined nucleus taking a pale basic stain and enclosing a sharply outlined metachromatic nucleolus (red with thionin, methylene blue, and

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with hematoxylin and eosin); with iron hematoxylin the nuclear body stains light blue, the nucleolus a blue black. No chromatin threads are to be detected in the nucleus. Scattered over the reticulum of the cell body in these intermediate examples are great numbers of chromatin granules, particularly well brought out by iron-hematoxylin, but also quite easily seen in specimens stained in Delafield's hematoxylin.[1] These are invariably coarser and generally proportionately more numerous the larger the unsegmented parasite. In these intermediate bodies the cell substance is usually somewhat shrunken away from the wall, but not invariably. With the development of these scattered chromatin granules the nucleus becomes less and less well defined, and tiny chromatic fingers grow out from the nucleolus, which is thus apparently the source from which the scattered granules are derived. As a succeeding change, going toward the production of sporoblasts, each of these chromatin granules becomes surrounded by a small amount of a hyaline plasma taking faintly the basic dyes. Apparently this occurs primarily centrally close to the site of the nucleus, which by this time has completely disappeared; and as the central spherules containing chromatic granules enlarge and grow into sporoblasts, the same changes proceed toward the periphery. (These spherules constitute practically all of the contents of the body marked "*a*" in Fig. 2, although the reproduction fails to show them well. They are better seen by examining with a hand lens the border zone marked "*e*" between the ruptured cell wall and mass of discharged sporoblasts in Fig. 4.) These spherules are only in a general sense spherical, showing minor irregularities in shape. Beginning centrally they soon grow into definite sporoblasts, the *fully developed parasite* (Fig. 1, *f*, Fig. 2, *a*) containing vast numbers, surely some thousands. These sporoblasts are spherical in shape and are provided with a smooth, unmarked, and apparently firm and dense wall. They vary but little in size, all being approximately 5 mm. in diameter. They are easily distinguished from the spherules by their size, uniform shape, and possession of a cell membrane, which more or less obscures the contents. The younger ones, as a rule, have a light blue tint with hema-

[1] Examine the bodies in Fig. 3 with a hand lens for better appreciation of this point.

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toxylin and eosin when seen on the surface, but by careful focussing one can make out the existence of an internal structure; the older ones with the same stain assume a somewhat metallic red color, and careful examination with high amplification shows (Fig. 5; or, better, Fig. 6) in the interior a number of small rounded spores clustered

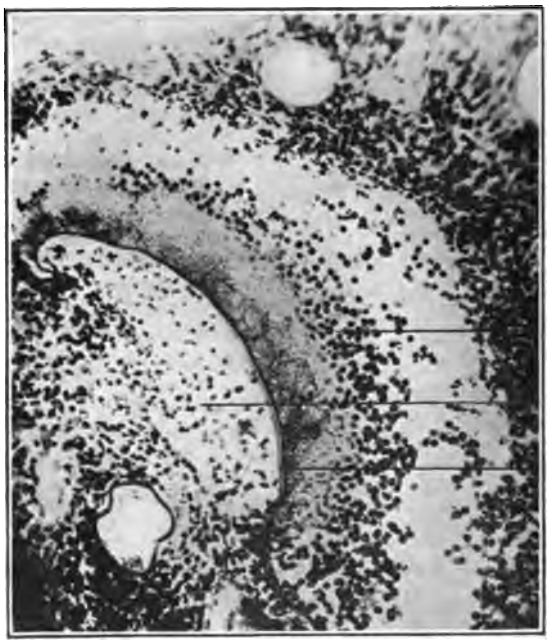

FIG. 4.—Higher amplification of ruptured body shown in Fig. 1, *d*, but taken from another of the serial sections and not presenting precisely the same outlines; *a*, developed sporoblasts set free by rupture of the parent wall; *b*, leukocytes outside the wall; *c*, the double-contoured and everted wall. Between *c* and *a* is a granular layer which is made up of the chromatin-bearing spherules which develop into sporoblasts.

together in a mulberry-like mass. The precise number of these spores is difficult to determine because of their minute size and the manner of their arrangement; but surely there are eight or more. The highest number which the writer has been able to confidently discover has been twelve; the constancy of any given number, however, while probable, cannot be asserted. These spores are particularly

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well brought out by iron-hematoxylin, each spore, and, too, the cell wall, taking a blue-black stain with this method of coloration.

The sporoblasts are retained within the parental cell wall until the latter, through internal pressure or other agency, is broken, and apparently possessed of considerable elastic retractility, may

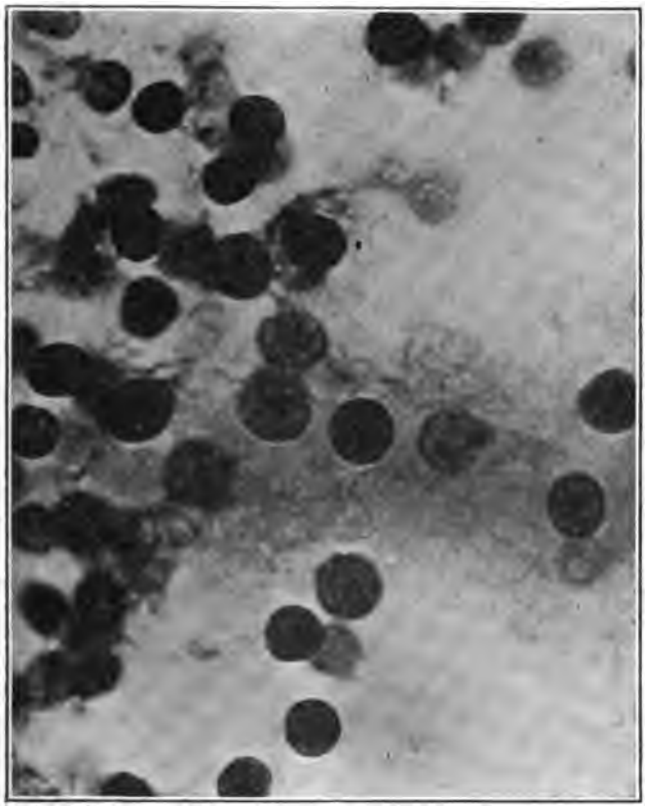

FIG. 5.—Higher amplification of sporoblasts shown in Fig. 4, *a*. Stained with hematoxylin and eosin and only partially showing the interior spores.

become quite everted (seen only in one instance in the specimens of the two cases, and shown in Fig. 1, *d*, and in Fig. 4). The possibility of discharge of the sporoblasts through a micropyle is frequently suggested by the appearance of a small area of flattening and lack of uniformity of structure of the wall of some of the bodies (note the

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lower end of each of the two well-focussed bodies in Fig. 3, and the similar appearance in the lowest body in Fig. 2). Nowhere in the specimens, however, could this be confirmed; but, on the contrary, in both specimens several ruptured or partly ruptured bodies were encountered, indicating splitting as the actual mode of release of the sporoblasts, and to the writer's mind the appearance of a micropyle is either the result of shrinkage or is susceptible of another explanation, to be suggested later.

FIG. 6.—Sporoblasts from the same position as in Fig. 5, but stained with iron-hematoxylin, and exhibiting more clearly the enclosed spores in a mulberry-like mass; *a*, sporoblast enclosing spores; *b*, a dehisced sporoblast, the inner half containing a number of spores, the outer only a single spore. The outer half of *b* is viewed in the concavity, the light passing through only one thickness of the wall; the inner half is seen from without and through two thicknesses of wall and is in consequence darker in the illustration than the half which has fallen away. (Photomicrograph made at slightly lower amplification than in case of Fig. 5.)

It is about these parent parasites, both before and after rupture of the wall, that special polynuclear leukocytic accumulation takes place to the formation of the miliary abscesses above mentioned, there being probably produced at this period of the cycle a special chemotactic substance, which is probably diffusible through the wall of the parent body and is also largely set free upon rupture of the wall, About the intermediate and younger bodies there are comparatively few of these cells, the tissues rather showing evidences of connective-tissue proliferation and a greater or smaller number of young endo-

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thelial cells and plasma cells. (This appearance is particularly evident in Fig. 1, the zones of cells about *f*, indicated by the reference line "*e*," and about "*d*" being polynuclear leukocytes. The cells enclosed in the everted wall of "*d*" are also of this type, and they are shown also in Fig. 4 by reference line "*b*." In Fig. 2, made from Dr. Carpenter's specimen, the leukocytic infiltration is denser and more diffused than in Fig. 1. It is well-marked about bodies *a* and *b;* and to the left of *b* is a third large area of accumulation which is peripheral to another dividing body not shown in the section from which the photomicrograph was made.) Probably the earlier forms are free from any important amount of diffusible toxic substance, and cause irritation and inflammatory reaction largely mechanically by their presence; but it may be suspected that in the course of division and sporulation endotoxins of a diffusible character are produced which induce the formation of the tiny abscesses, and which should, were there a greater amount present and absorbed, lead to systemic reaction and the appearance of general symptoms.

Returning to the discharged sporoblasts and their contained spores, it must be acknowledged that thence onward their fate has not been certainly traced in the specimens in hand. However, the following appearances have been noted, which are compatible with the known history of reproduction of a number of the fungi, and show analogies to that of myxomycetes and coccidia. Among the developed sporoblasts there may now and again be found examples which are broken into approximately equal parts, which have, in other words, dehisced (Fig. 6, *b*). No other appearances which could explain the emergence of the spores have been noted after prolonged search in variously stained specimens. Scattered among the sporoblasts and in the tissue about the ruptured parasite are to be seen numerous deeply chromatic granules, which possibly are the escaped spores; but none of these have the flagellate or amebiform appearances of the spores of which the writer is cognizant. Their identity is open to confusion with fragmented nuclei of leukocytes or other degenerating cells of the vicinity, and with the spherules of the parasite not as yet developed into complete sporoblasts, as well as possibly remnant granules from the reticulum of the parent body. Here and there widely in the tissue are met non-nucleated bodies varying in size, but larger than

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these granules or than the spores, staining but feebly with the basic dye, often more or less vacuolated and varying in shape and often distinctly amebiform in outline. It might without difficulty be thought that these have developed from the spores after dehiscence of the ripened sporoblasts, that they exist for a time as naked ameboid bodies, and that coming to rest they gradually assume the definite wall of the young bodies commonly seen in the sections—the wall at first thin and simple and the substance plasmatic and faintly attracting the basic stain; the wall later becoming of thicker and double structure, the nucleus forming and the substance becoming reticulated—and still later the chromatin of the nucleus increasing and becoming distributed upon the reticulum in the form of the chromatin granules above described. (The possibility of such non-nucleated protoplasmic bodies being merely sectioned parts of various cells must, however, be acknowledged.)

Such a mode of development (tentatively accepting as correct the apparent but not fully established stages between the escape of the spores from the sporoblasts to the earliest established forms of the parasite) bespeaks the likelihood of a sexual reproduction. In this connection reference may again be made to the peculiar flattened area seen in a number of the spherical parasites (Fig. 3, at lower pole of each of the well-focussed round bodies in the illustration), which might well be a micropyle for the entrance of fertilizing elements, such spherical bodies thus being assumed to be female or *oögonia*. If this be true, the further suggestion easily follows (although of course it is only a surmise, no actual evidence being appreciated to substantiate the view) that the bodies presenting a crescentic appearance in section (Fig. 1, *a*), instead of being merely collapsed specimens, are in reality male organisms, *antherids* (conforming with the cup shape of the antherids of various fungi). It would be necessary to assume, in such a supposition, that there has been a suppression of a mycelium, as this mode of reproduction among the fungi particularly occurs in the higher types, as among the mucors, and some of the higher ascomycetes, as the *spheriaceæ*. That in parasitism in animal tissues such a suppression of mycelium does occur is clearly evident from the frequent growth of mycelial fungi from the monocellular organisms of cases of blastomycosis.[1]

[1] Ricketts, supra cit., and others.

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It is to be noted that no appearance in the least suggestive of budding is evident in any of the preparations from these cases, and that apparently a rather complex spore production prevails. Were this surely constant it would definitely eliminate the specimens from the blastomycetes, a name originally coined to cover all monocellular fungi reproducing by budding. While there is no evidence that budding does take place, of course it cannot be entirely ruled out; but with the details above given it seems very probable that both the saccharomycetes and the torula forms may be excluded from further consideration. So, too, the size of the organisms (far larger than any thus far recorded in the cases of blastomycetoid infection) and the complex sporulation do not permit one to consider seriously the oidia and similar low types of moulds. While certainly the general plan of production is very similar to that of coccidial multiplication, and many of the staining reactions suggest this type of organisms, a centripetal (rather than a centrifugal) development of the sporoblasts would have been probable and some more definite approach to the frequent crescentic shape of sporozoites might have been expected were these organisms coccidia. The source of the infection, in case from dirt forcibly introduced into the conjunctival tissues, is on the whole suggestive of the parasites belonging to the vegetable rather than of such special (obligate parasitic) protozoa as coccidia.

Finally, while there exist general analogies of these bodies to the blastomycetic and blastomycetoid parasites thus far described both in general structure and appearance, their size and the complex reproductive changes distinguish them clearly from the distinct blastomycetes and the lower mycelial fungi; but beyond referring them to the general group of the higher fungi, as perhaps spheriaceæ or possibly to some myxomyces (probably here materially altered by parasitism), we are at present unable to fix their identity, and must await opportunity in some future case to obtain information by culture studies as to the vegetative characters of the bodies described.

NOTE.—The peculiarities of these organisms so clearly differentiating them from the parasites thus far published under the name of *coccidiaides* and *blastomyces* make it, we feel, undesirable, save for purposes of comparison, to attempt any extensive bibliographic list.

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For such purposes we would refer to the articles of Ricketts,[1] Nichols,[2] Weiss,[3] Brown,[4] and Montgomery and Ormsby,[5] to most of which articles is appended a more or less extensive list of references bearing upon blastomycetic and blastomycetoid parasitic organisms.

As special references to the discovery of such parasitic organisms in the conjunctiva and the neighboring tissues (but in no instances presenting types with the characteristics here described) may be mentioned Wood,[6] Wilder,[7] and Lundsgaard.[8]

May 14, 1908.

Periarteritis Nodosa, with Report of a Case with Autopsy.

By WARFIELD T. LONGCOPE, M.D.

Periarteritis nodosa, though a very rare disease, is nevertheless of much interest, by reason of its unknown etiology, on account of the discussions which have arisen as to the histogenesis of the nodules, and because a successful diagnosis during life may prevent or postpone the fatal issue.

The following case occurred in the service of Dr. James Tyson, at the Pennsylvania Hospital, to whom I am indebted for the use of the history.

The patient, a colored man, aged thirty-five years, single, and a stevedore by occupation, walked into the receiving ward on September 26, 1907, complaining of precordial pain, dyspnea, and edema of the abdomen and lower extremities. His family and past history were unimportant. He drinks tea and coffee moderately, beer freely, whisky and gin occasionally. He smokes considerably, ten to fifteen pipes a day; cigars occasionally. He has had gonorrhea twice, the last attack six months ago.

[1] Journal of Medical Research, vol. vi, o. s., p. 373.
[2] Ibid., vol. vii, o. s., p. 312.
[3] Ibid., p. 280.
[4] Journal of American Medical Association, March 2, 1907.
[5] Archives of Int. Med., August 15, 1908, vol. ii, p. 1.
[6] Annals of Ophthalmology, 1904, vol. xiii, p. 92.
[7] Ibid., p. 897; Journal American Medical Association, December 31, 1904.
[8] Klin. Monatsbl. f. Augenheilk., 1890, vol. xxxviii, p. 13.

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The present illness began about three weeks before admission with pains in the joints and calves of the legs, slight malaise, and weakness; his appetite was poor and his bowels slightly constipated. There was no headache, vertigo, or epistaxis; no cough, though he expectorated occasionally. There were no pains in the chest. He has not had abdominal pains or tenderness. He continued to work up until two weeks ago, when he had to quit and go home to bed, where he remained for two days, when he felt better and got up. He remained around the house until his condition became worse again, and he was compelled to go to bed. Four days before admission he noticed that his legs were beginning to swell; that he had become quite dyspneic, and had precordial pain, anorexia, and nausea, with constipation. On admission, his temperature was 96°; pulse, 56; respiration, 28.

Physical examination showed that the patient is a well-developed, fairly muscular looking colored man; lying quietly in bed, though showing moderate dyspnea. His skin is cool and slightly moist. His pupils are equal and react to light. The conjunctiva are clear. The tongue is well coated, slightly dry, and tremulous. His breath is fetid. No pulsation of vessels of the neck are to be seen. The submaxillary glands are slightly enlarged and tender, more so on the right side. The chest is well developed, muscular, and symmetrical; the expansion is good. The lungs show no impairment of resonance, and there is fair vocal fremitus. Several scattered mucous rales are heard throughout both lungs, though normal vesicular breathing is heard everywhere.

Cardiac dulness reaches the upper border of the second interspace and extends 4 cm. to the right of midline. P. M. I. is in the fifth interspace, 10.5 cm. to the left of midline; impulse is faint, diffuse, and almost imperceptible. The heart sounds are fairly clear, forcible, and well heard at all cardiac areas, but somewhat rapid; at the apex there is a moderately soft, rough, systolic murmur transmitted toward the base. It does not replace the first sound. At the base the murmur is only faintly heard and the second sound is accentuated.

The radial pulse is of small volume and tension, and seems quite thready and at times irregular. The abdomen is tense and distended, slightly edematous, and pits on pressure. It is somewhat tympanitic in the epigastric region, while dulness is more pronounced in the lower

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quadrants. There is some tenderness and sensitiveness over the liver, but no pulsation. The liver dulness extends from the fourth rib to 3.5 cm. below the costal margin. There is slight edema of the penis and scrotum. The inguinal glands are slightly enlarged. There is moderate edema of the lower extremities. The leukocytes number 13,200.

September 27. The urine is clear, reddish yellow, acid, of specific gravity 1020, shows a trace of albumin, no sugar, numerous hyaline and finely and coarsely granular casts. There are a few leukocytes, epithelial cells, amorphous urates, mucus, and detritus.

For a time the patient seemed to improve, there was less dyspnea, the rales disappeared from the chest, and he felt more comfortable. During his illness the temperature was slightly and irregularly elevated, reaching at times 101° F. On September 29 the white blood cells numbered 11,250. On October 10 the urine suddenly became bloody, and contained many granular and hyaline casts. From this time on the blood was found sometimes in large quantities, sometimes in microscopic examination off and on, with varying quantities of albumin. On October 10 a gallop rhythm was noted when listening over the region of the apex beat of the heart, and the spleen was palpable. Blood appeared off and on in the urine. On October 14 the leukocytes numbered 22,600. The Widal reaction was negative. Dyspnea made its appearance off and on during the course of the illness. On October 25 the leukocytes numbered 30,000, the hemoglobin was 58 per cent. On the night of the 26th the patient became very dyspneic, the pulse weak, rapid, and at times almost imperceptible, and the heart sounds were barely audible. The next day the patient was somewhat better, but died in another attack of the same kind during the day of October 27.

The autopsy was performed twenty-five hours after death. The following is a brief abstract of the protocol:

The body is that of a large and somewhat wasted negro, 166 cm. in length. There is moderate rigor mortis. The pupils are equal. There is no visible postmortem discoloration. The external genitalia are apparently normal. There is no edema of the extremities.

The peritoneal cavity contains 50 c.c. of a clear fluid, but shows nothing else abnormal.

The thorax and pericardial cavity show no abnormalities.

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The heart weighs 450 grams. It is increased in size. The pericardium shows some diffuse thickening and is slightly opaque. Over the vessels there is a very marked white thickening. This is most noticeable over the right ventricle. There are no adhesions, and the general surface is smooth and glistening. No antemortem thrombi can be found. The foramen ovale is closed. All the valves are thin, delicate, and apparently normal, but the cavities of the left side are definitely dilated, while the wall of the left auricle is thickened. The left ventricle averages 12 to 18 mm. in thickness. The heart's flesh is very firm, and on section has a granular, yellowish appearance. Near the apex there are grayish or yellowish streaks in the muscle. The aorta is quite delicate. The coronary arteries, so far as they can be followed, are delicate and patulous and have very smooth walls.

The lungs show edema, congestion, and some bronchopneumonia.

The spleen weighs 100 grams and measures 12 x 7 x 31.5 cm. The spleen is small, regular, and firm. The cut surface is rather pale and the trabeculæ and vessels prominent.

The liver weighs 1780 grams and measures 28 x 19 x 9 cm. The liver is quite large, regular, and firm. The surface is smooth, the capsule delicate, the color mottled light brown and purple. On section the cut surface has a curious coarse mottled appearance. It is generally smooth, cloudy, and brownish gray, but scattered irregularly over the entire surface, from periphery to hilum, there are irregular, red, well outlined patches, varying from 0.5 to 2 cm. in diameter. Some are slightly depressed. The connective tissue in a certain number of the portal spaces seems increased, and in some places the vessels look very thick. The lobules are only partly defined. On making several cuts through the liver, small arteries are found which are plugged with firm red thrombi. The arteries at the hilum are patulous. The gall-bladder is apparently normal and the bile ducts patent.

Both kidneys weigh 380 grams. The left kidney measures 13 x 75 x 5 cm. It is large, firm, and regular. The capsule strips with some difficulty, leaving a rather rough surface, mottled irregularly purple, yellow, and red. There are irregular yellow patches surrounded by a red zone, seen in many places, which vary from 0.5 to 2 cm. in diameter. On section the cut surface shows a markedly mottled appearance.

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It is often difficult to distinguish the medulla from the cortex. The cut surface is mottled irregularly yellow and red, and in the cortex, particularly about the ridge, there are great numbers of irregular, opaque, yellow pyramidal patches extending 1 to 2 cm. into the kidney substance, surrounded by deep red lines and sometimes an indefinite red zone. Other smaller areas, which are like these but less definite, are scattered everywhere through the cortex. The medullary pyramids are swollen and red. The cortical substance, though it is very irregular, can sometimes be made out between areas of necrosis. Here it measures about 1 cm. in thickness. The striæ are entirely obliterated. Occasionally small red and white dots are seen, which may be glomeruli.

The most interesting condition concerns the *bloodvessels*. The main renal artery and the larger branches leading to the kidney are all patulous and appear perfectly normal. On following these branches toward the periphery, almost every vessel is found to be plugged some place during its course by a firm red or white thrombus. The thrombi are first observed in the arcuate arteries, and extend, often, as far as the vessels can be followed. The calices show no marked changes. The pelvis has a double ureter which extends as far as the bladder, opening by two orifices into the bladder.

The right kidney measures 19 x 5.5 x 4 cm. Though smaller than the left, the right kidney is practically like it. On section the cortical portion is slightly paler and there are not so many infarctions. The artery at the hilum, as well as its branches, is apparently normal, but the arcuate arteries, or at least many of them are thrombosed in exactly the same manner as the vessels in the left kidney. The ureter and pelvis are apparently normal. Both renal arteries are normal from the hilum of the kidney to the entrance into the aorta.

The intestines show congestion through the ileum, and in places fine red lines, looking like thrombosed vessels, are seen beneath the mucosa.

The larger branches of the aorta and the mesenteric arteries are delicate and patulous.

The iliac vessels are free from thrombi.

The brain is of moderate size. There is some congestion and edema of the pia. When it is removed the entire left occipital lobe is found to be soft, shrivelled and yellowish brown in color. On

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section this region shows the most extensive softening and necrosis. The central portion is entirely diffluent. The posterior cerebral artery, which leads to this region of the brain, is found to be plugged throughout a greater portion of its length by a firm red and gray thrombus mass. The cerebellum, pons, and medulla are apparently normal.

The stomach, esophagus, adrenals, pancreas, urinary bladder, prostate, seminal vesicles, larynx, trachea, thyroid, and lymph nodes showed no gross changes bearing directly upon the condition.

The microscopic examination of the various organs showed the changes typical of periarteritis nodosa in the smaller arteries of the heart, liver, kidneys, pancreas, testicles, brain, perineural connective tissue, and voluntary muscles. There were anemic infarctions of the kidneys, foci of necrosis in the myocardium and liver, typical glomerular nephritis, degeneration of voluntary muscles, and edema of thyroid. It is greatly to be regretted that cultures made from the organs at autopsy were accidentally destroyed.

A study of the arteries affected by this peculiar disease soon revealed the fact that the bloodvessels presented widely different appearances, depending upon their size and the part of the nodule through which the sections were made. The arteries of the myocardium, the liver, kidneys, pancreas, voluntary muscle of the leg, the small vessels in the tissue of the neck and testicles, all show varying grades of the condition about to be described.

The most extensively developed lesions are seen in the larger vessels of the liver and kidneys. A longitudinal section through one of these nodules, invading a large artery in the kidney, shows the following appearance: Above the nodule the vessel wall appears normal, except for some slight thickening of the intima, on one side, and occasional vacuolization of the muscle fibers of the media. As one approaches the nodule, the first changes are to be seen in the adventitia, where there is a slight infiltration with small round cells, a few polymorphonuclear leukocytes and eosinophiles. At a very short distance from this beginning change in the adventitia, alterations are to be seen in the intima. Covering the slight fibrous thickening there are cells of several types. Most of them are large polygonal cells, with irregular, palely staining nuclei or long tapering spindle cells, which resemble fibroblasts. Somewhat nearer the nodule

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the media shows swelling of the muscle cells with loss of nuclei, and at the very margin the media and elastica make a sharp curve outward looking exactly like the brim of an aneurysm. At this point, the inflammatory and infiltrative changes, both in the adventitia and intima, become more marked. At the edge of the sharp bend in the media, sections stained in Weigert's elastica show a sudden break and complete destruction of the internal elastica with a corresponding disappearance of the external elastica and elastic fibers of the adventitia. The media beyond this point is thinned and replaced by infiltrating fibrin and polymorphonuclear leukocytes. This line, which forms a continuation of the media, quickly tapers away and disappears, at which point the inflammatory tissue, replacing the adventitia and media, more or less fuse. The new tissue, taking the place of the intima, which is composed of large polygonal cells and long, tapering, spindle cells, separated by a good deal of intercellular substance and mixed with polymorphonuclear leukocytes, small round cells, and a few multinucleated giant cells, entirely fills the aneurysmal dilatation formed by the break in the media and elastica, and encroaches even, to a slight degree, upon the lumen of the vessels. The wall of the vessels, directly opposite to the nodule, shows no bulging or aneurysmal formation, but shows the same, though milder grade of proliferation and inflammation of the adventitia and intima. The internal elastica lamina is perfectly preserved, but a few small breaks are seen in the external elastica with occasional vacuolization of the fibers of the media. Just above the nodule the vessel branches, and several similar nodules are found upon the main vessel and its branches. Some of these involve the entire vessel, others affect only one side of the vessel. Sections, through some of these large nodules, show that the proliferative and inflammatory process, taking the place of the intima, entirely occludes the vessel lumen. In other places an aneurysmal dilatation is only partly filled by these new formed cells, while the remainder of the cavity is obliterated by a thrombus mass, usually composed of fibrin, platelets, polymorphonuclear leukocytes, and a few red blood cells. In old lesions the thrombi show beginning or complete organization.

In serial longitudinal sections made through these large vessels, one sees at times two nodules along the course of the vessel involving all of the walls, but separated for a short distance by a stretch in which

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the intima and adventitia are principally affected. In these stretches there is no dilatation of the vessel. The intima shows irregular and more or less extensive proliferation and inflammatory change, such as has already been described, while the adventitia is infiltrated diffusely with small round cells, epithelioid cells, and polymorphonuclear leukocytes. The internal elastica is well preserved. The media, in places, shows swelling and vacuolization of the muscle fibers with loss of nuclei. In localized areas, along the vessel in such places, one sees small foci of necrosis with outward bulging of the media. The elastica interna is destroyed, the media is extensively infiltrated with fibrin, polymorphonuclear leukocytes, and a few of the large pale cells which seem to enter the muscular coat from the thickened intima and adventitia. About such area the adventitia shows particularly well-marked proliferative and inflammatory changes.

Cross-sections through other large, well developed lesions show the same changes from a different view point. Serial sections made through various nodules in this direction show always at the periphery of the nodule, involvement, first of the adventitia, then the intima, and finally more or less complete, but often irregular, destruction of the internal elastica and media. Some of the vessels show general irregular dilatation of the vessel, others show bulging on one side; occasionally the lumen is partially occluded by proliferation and infiltration of the cells of the intima; in other sections the lumen is plugged by a thrombus mass composed of red blood cells, polymorphonuclear leukocytes, fibrin, and platelets. These thrombi, like the changes in the vessel walls, are localized, and may be confined to a very limited portion of the vessel lumen.

In a few of the vessels, especially in one of the small branches of the coronary artery, the proliferation of the cells of the intima was found, in serial sections, to extend along the vessel for really a great distance, away from the nodule. The thickened intima almost occluded the lumen of the vessel. It had a vacuolated appearance, and was composed chiefly of young connective-tissue cells, with here and there a small lymphocyte or polymorphonuclear leukocyte. The endothelium did not participate, for the endothelial cells could be seen as a line, broken in only one or two places and covering the thickened intima. The internal elastica was broken in places, and

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immediately beneath it an increase in cells of the subintimal connective tissue could be seen. The muscle cells of the media were swollen, pale, and granular, and here and there small focal accumulations of polymorphonuclear leukocytes and small round cells were seen. The adventitia was the seat of some edema and diffuse infiltration by a few epithelial cells, small round cells, and polymorphonuclear leukocytes.

In the older lesions the inflammatory changes were not so prominent, and the vessel wall was converted into a wide, circular ring of cellular connective tissue, in the centre of which was an organizing thrombus. In some of these nodules, which are evidently undergoing the process of healing, not a vestige of the original smooth muscle of the media or elastic tissue of the internal or external elastica can be found with Van Gieson and Weigert stains. In other nodules fragments of elastic tissue or a few bundles of smooth muscle fibers are visible.

The lesions in the small vessels, which differ in many respects from those in the larger vessels, could be studied best in the voluntary muscles. In serial sections it can be seen that the nodules, though sometimes found along the course of a vessel, are usually clustered in definite regions which correspond to the bifurcation of arteries. At some distance from the nodule, in many instances, the perivascular lymphatics are seen to be distended with polymorphonuclear leukocytes and large phagocytic cells of the epithelioid type. As one approaches the nodule, the adventitia of the vessels, as well as the perivascular connective tissue, shows some edema and infiltration of the polymorphonuclear leukocytes, epithelioid cells and small round cells. This inflammatory exudate increases, becoming denser and showing some infiltration with fibrin, and the presence of the large pale cells described before, until it forms a wide zone about the muscular ring of the media, which at the margins of the nodules never showed any changes. In sections made at varying distances from the margin, the endothelium of the intima shows swelling the intima itself is greatly swollen and shows an infiltration of polymorphonuclear leukocytes, fibrin, and large, pale cells. The fibrinous exudate in the intima increases in thickness and density, forming in the smallest vessels a granular looking ring, staining pink in eosin, and situated internal to the media. Gradually the media is involved in the inflammatory process; it becomes narrow, the circle is increased

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showing a dilatation of the vessel, the muscle cells become pale and granular, the coat is infiltrated with polymorphonuclear leukocytes, fibrin, and the large irregular cells, and finally in the centre of all the nodules of any size the coat is entirely destroyed.

Here the ring of fibrin, which has gradually replaced the intima, makes a very conspicuous feature. It forms a zone of varying thickness, sometimes covered with endothelium, hyaline in appearance, and in the larger vessels assuming a yellowish tint when stained in eosin. In the smaller vessels the ring stains brilliantly with Weigert's fibrin stain, while in the larger vessels, though the periphery stains deeply in the fibrin stain, usually a central core remains entirely or partly unstained. A cross-section made through the centre of such a nodule shows a lesion which may be divided into several zones. Forming the innermost zone is a hyaline ring of fibrin, upon which may be seen a few endothelial cells, fragmented nuclei, or polymorphonuclear leukocytes. Outside of this is a zone composed chiefly of the large irregular cells with basophilic protoplasm, infiltrated with polymorphonuclear leukocytes and eosinophiles, and tree-like branches of fibrin projecting out from the central hyaline ring. Beyond this, again, is the connective tissue of the adventitia, densely infiltrated with polymorphonuclear leukocytes, eosinophiles, small round cells, and epithelioid cells. No trace of the original vessel wall is left.

In many of the nodules upon the smaller vessels the midzone, replacing the media, is very well defined, and it was possible to trace through serial sections the probable origin of some of the large, irregular, slightly basophilic cells, with pale vesicular nuclei which form such a conspicious feature of the zone. It could readily be made out by the aid of Mallory's connective tissue stain and Weigert's elastica stain, that this midzone lay between the remains of the internal and external elastic lamina, and therefore represented the region of the media, though it was perhaps three or four times as wide as the media of the normal portion of the artery, while the lumen of the vessel was proportionately enlarged.

As one approaches in serial cross-sections from the periphery to the centre of a small nodule, the first changes noted in the muscular coat are swelling of the muscle fibers, with faint granulation of the protoplasm and enlargement of the nuclei. The fibers then become

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slightly separated, first toward the external margin of the media. The nuclei, at the same time, assume an oval, broad appearance. At this stage, in one section, karyokinetic figures were found in the smooth muscle cells. In sections a little closer to the centre of the nodule, the outlines of the cell become distinct, and a few cells, which are quite broad and oval in shape and the protoplasm of which stains faintly in hematoxylin, are seen. The appearance of the smooth muscle cells now changes entirely. The cells assume an irregular contour, the protoplasm stains definitely in hematoxylin, the nuclei become irregular, more or less lobulated, and reach a size four or five times as great as that of a polymorphonuclear leukocyte. During the transformation of these cells, small lymphocytes, eosinophiles and polymorphonuclear leukocytes appear between them, and finally at the centre of the nodule the wide midzone is formed, which bears no resemblance to the media of the normal bloodvessel.

In the nodules which are apparently older, there is much connective-tissue proliferation, and the polymorphonuclear leukocytes are often replaced by great numbers of plasma cells and epithelioid cells.

The pathological changes in the nodules have been so minutely and exhaustingly described by others that it is needless here to enter into a discussion of this subject. It is only necessary to draw attention to the alterations observed, in the present case, in the muscular coat of some of the smaller vessels. From the appearances which have already been described, one gained the impression that the smooth muscle cells actually formed a part of the proliferative changes seen in the middle zone of the nodule. In a few instances karyokinetic figures were seen in cells which could still be recognized as smooth muscle cells, and though it was obviously impossible in advanced lesions, even with special stains, to differentiate many of the large irregular cells forming a part of this middle coat from the cells which seemed to arise from the fixed connective-tissue cells and invaded the walls of the vessels, still in the early stages of the disease or at the margins of the nodules, what appeared to be a definite proliferation and transformation of the smooth muscle cells could be followed.

The two points which have been most discussed and which as yet have remained unsettled are the histogenesis of the nodules and the etiology of the disease. When the disease is fully developed all the coats of the arteries are involved, and, as Ferarri and others have

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contended, the condition is really a polyarteritis. Indeed, it is this very tendency of the disease to involve all the coats of the vessel wall which has made it so difficult to determine the primary point of attack.

The study of the histogenesis of the nodules is fraught with the greatest difficulty, for the disease seems to spread so rapidly from one coat to another, that it is only in the very smallest nodules or in material obtained after a short illness, that one can come to any decision as regards the position at which the vessel is first attacked. In the present case many sets of serial sections were made through portions of the liver, the kidneys, and voluntary muscles, in hopes that some light might be thrown on this question. In the large vessels the disease was so far advanced that all three coats were extensively involved. The same thing was also true of most of the nodules situated along the course of the small vessels. In a few nodules the intima showed only a slight edema or appeared normal, but in almost all both the media and adventitia were extensively involved. Even in the very smallest nodules on minute arteries, nodules which ran through but six or seven sections, both adventitia and media were involved. In two instances, however, the adventitia about minute arteries showed a localized infiltration of small round cells, without being demonstrable either in the muscle coat or in the intima. Whether or not these were actually beginning nodules, it was extremely difficult to say, for except for the perivascular infiltration there were no other changes by which one might identify the condition as an early nodule. Since, however, in several definite nodules upon minute arteries the same accumulations were observed in the adventitia plus a degeneration of the media and slight localized bulging of the vessel, one is inclined to regard these perivascular accumulations of small round cells as the beginning of a nodule. In not a single instance was it possible to find degenerative changes in the muscular coat without comparatively extensive inflammatory changes of the adventitia.

In the present case it seems very likely that the adventitia of the arteries was the primary point of attack for the disease, but it is not certain that this explanation will apply to all cases; and in any event the extension to the media must take place with great rapidity. It is even possible that the etiological agent may reach the media by

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way of the perivascular lymphatics and vasa vasorum without producing marked alterations in the adventitia.

The cause of the disease, however, is even more obscure than the histogenesis of the nodules. By some it is thought to be due to syphilis. In the present case, though series of sections from several nodules in the kidney were stained by the Levaditi method, no spirochetæ could be discovered. Both Schmorl and Benedict have suggested, since their patients improved upon doses of iodides, that the disease might be syphilitic.

By some, it has been thought that the disease was purely of mechanical origin; but, although there are no observations to substantiate the claim, most authorities are of the opinion that the disease is caused by an acute infection or intoxication. With one exception, where cultures have been made from the organs at autopsy, no bacteria have been found. Bombard, in a recent case, obtained staphylococcus albus in cultures from the kidney and spleen. Sections stained for bacteria have in all cases, so far, yielded negative results. In the present case cultures made from the kidney and spleen were most unfortunately destroyed by accident. Sections of the kidney stained by the Weigert-Gram method showed a few groups of cocci in chains, but they seemed to bear no relation to the nodules, and were not found in the other organs or in the nodules in other situations. A modification of the Romanosky stain was also employed, but no bacteria could be found in the tissues by this method.

In spite of this constant failure to demonstrate bacteria, there are many features of the disease which suggest that it is an acute infection. The fever, the leukocytosis, which, though not invariable, is quite common, and the type of inflammation involving the wall of the vessel, rich in polymorphonuclear leukocytes, eosinophiles, and fibrin, all point to an infectious origin.

Finally, the glomerular nephritis, so commonly associated with acute infection, which, as found in the cases of Hart and Bombard and was present in my case, suggests again that the periarteritis nodosa is caused by some intoxication or unknown infectious agent. Certainly syphilis cannot at present be accepted as the only etiological agent.

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Cysts of the Common Bile Duct.

BY R. S. LAVENSON, M.D.

(From the Pepper Laboratory of Clinical Medicine of the University of Pennsylvania.)

THE following case was, clinically and pathologically, of unusual interest: P. R., a school girl, aged eight years, was sent to the University Hospital on account of persistent jaundice and an abdominal tumor. She was admitted to the service of Dr. Charles H. Frazier, to whom I am indebted for permission to use the clinical data. The following notes are abstracted from the patient's history on admission to the hospital:

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Family History. Father and mother are both in good health. Three other children are living and well. One child died of cholera infantum. Father had a sore on his penis sixteen years ago. His physician cauterized it and gave him medicine during the ensuing year. There were no subsequent manifestations, and he has been well ever since. Mother had one miscarriage, about four months ago. The patient's maternal grandfather and paternal grandmother died of carcinoma of the stomach.

Social and Previous Medical History. The patient has been going to school for the past three years, and until about one year ago was always bright, strong, and active. She has had none of the acute infections of childhood, and has always been considered a healthy child.

History of Present Illness. About a year ago the patient began to be jaundiced. This jaundice was unaccompanied by pain or other manifestations of illness, except for occasional attacks of nausea. The jaundice has been persistent and has gradually progressed in severity. With the increase in the jaundice the patient's appetite has deteriorated, and there has been a moderate loss in weight. For the past eight months the stools have been clay-colored and the skin itchy. Three weeks ago the mother noted a large mass in the middle and right upper quadrants of the abdomen. The mother is sure that she would have noticed it had it been present before then. She can give no information as to any increase in size since it was first noticed. The child complains of no pain or other discomfort, and sleeps well. There are no symptoms referable to the cardiovascular, nervous, respiratory, or genito-urinary systems.

Physical Examination. The patient is a well-formed, rather poorly nourished girl of normal size for her years. She has a bright intelligent expression. The skin of the entire body, the visible mucous membranes, and the conjunctivæ have an intense, bright icteric hue. There are no superficial glandular enlargements. The pupils are equal and react promptly to light and accommodation. The tongue is clean and moist, and the teeth are in good condition. The examination of the heart and lungs reveals no abnormalities. The upper border of liver dulness commences at the upper border of the fourth rib in the right midclavicular line. The sharp edge of

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the liver can be distinctly palpated about one-half inch below the costal margin. Commencing immediately below the edge of the liver is a protuberant mass extending from the right midaxillary line to one and one-half inches below and one and one-half inches to the left of the umbilicus. It is flat to percussion, is not tender, and moves downward with inspiration. It gives the impression of being cystic. There is tympany to the right, below, and to the left of the mass. Inflation of the colon shows that organ to be situated below

FIG. 1.—Showing the margin of the ribs and the boundaries of the tumor.

the mass. The palpating finger is easily inserted between the tumor and the edge of the liver. Pressure has exerted such influence on the lower right portion of the thorax as to produce marked shortening and elevation of the margin of the ribs on that side. This can be seen in the accompanying photograph (Fig. 1), in which the margin of the ribs and the boundaries of the tumor have been outlined. The spleen is not palpable and no alteration in the size or position of the kidneys can be determined.

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Urinalysis. Deep amber; light flocculent precipitate; acid; specific gravity, 1030; albumin and sugar negative; bile pigments positive.

Blood. Hemoglobin, 79 per cent.; erythrocytes, 4,190,000; leukocytes, 11,870. Differential count: Polymorphonuclear neutrophiles, 60 per cent.; lymphocytes, 23 per cent.; large mononuclear leukocytes, 15 per cent., transitional cells, 2 per cent.

Feces. Clay-colored; solid; faintly acid; normal odor; small number of leukocytes and epithelial cells; moderate amount of casein; occult blood negative; faint trace of urobilin.

Two days after admission to the hospital the patient was operated on by Dr. Frazier. When the mass was exposed it was found to be a cyst about the size of an ostrich egg. Coursing over its ventral surface was the stretched and flattened duodenum. The cecum and appendix were adherent to the lower pole of the cyst. The first impression was that the tumor was a cyst of the gall-bladder, but on further exploration the slightly distended gall-bladder was found lying between the cyst and the lower surface of the liver. A cannula was introduced into the cyst and about a quart of fluid resembling bile drawn off. It was then thought that the condition might be a cyst of the common duct—a view that was soon confirmed by further exploration. The adhesions were freed, the pedicle tied, and the sac removed. A dressed tube was fastened in the gall-bladder and a Mikulicz drain inserted into the wound alongside of it. In spite of vigorous stimulation, the patient failed to rally after the operation, and died three days later.

Autopsy. The autopsy, limited to the parts involved in the operation, confirmed the fact that the tumor was a cyst of the common duct. It measured 15 x 8 x 7 cm. (Fig. 2). The wall averaged about 2 mm. in thickness. The internal surface presented a peculiarly mottled appearance, by reason of the distribution of smaller and larger, irregularly shaped, brownish green areas on a yellowish white background. Microscopically the wall was seen to be composed of dense fibrous tissue, with an external peritoneal covering. The dark areas on the inner surface showed themselves to be more richly vascularized than the surrounding areas, and to contain deposits of bile pigments. The gall-bladder was slightly dilated;

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it was prevented from participating in the dilatation of the common duct by the partial obliteration of the cystic duct, resulting from compression by the cyst. The hepatic ducts were also slightly dilated. The portion of the common duct between the cyst and the duodenal papilla presented itself as a firm cord-like structure, the size of a goose quill in diameter. The extramural portion measured 1 cm. in length, and was patulous; the intramural portion, which measured 2 cm. in length, was entirely devoid of a lumen. Micro-

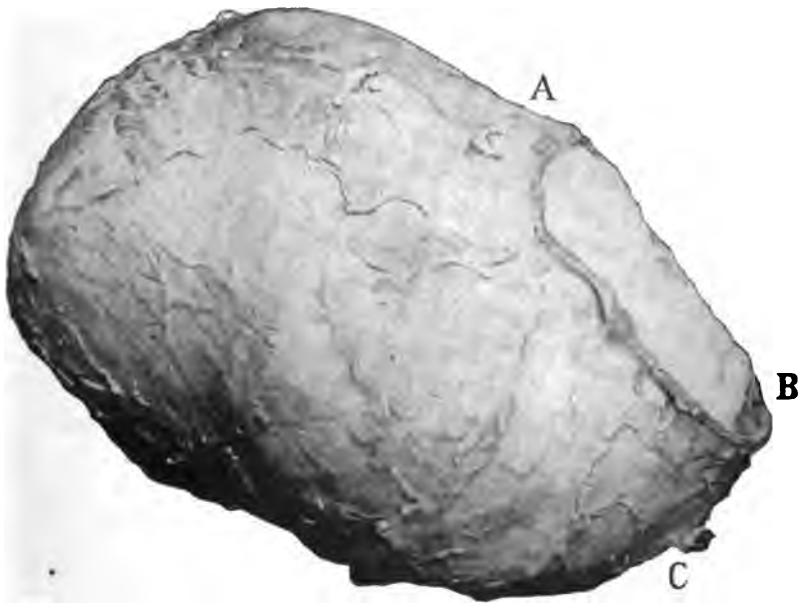

FIG. 2.—Photograph of the cyst (two-thirds natural size). *A*—*B*, the opening of the cystic and hepatic ducts into the cyst; *B*—*C*, the left wall of the common duct, forming the left wall of the cyst; *C*, the peripheral end of the common duct.

scopic examination of the latter portion revealed extensive fibrosis, with complete obliteration of the lumen and disappearance of all traces of epithelial elements. No opening could be found from the duodenal papilla into either the common bile duct or the duct of Wirsung, and as far as could be determined the latter suffered the same obliteration as the duodenal portion of the common duct. This view was substantiated by the histological examination of the pancreas, which showed advanced chronic perilobular pancreatitis.

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The liver was large, hard, and of a dark-green color. The surface was coarsely granular. Microscopically, changes characteristic of a biliary cirrhosis were seen: marked perilobular fibrosis, moderate intralobular fibrosis, dilatation of some of the intrahepatic bile ducts, and great proliferation of bile canaliculi.

I have collected twenty-eight cases of retention cysts of the common bile duct from the literature. Some of the reports are so meagre as to make them of interest only in so far as to put the case concerned on record. Others are more elaborate, and, with the case herein reported, permit the compilation of some interesting data bearing upon the condition.

Of the 19 instances in which the sex is mentioned, 17 occurred in females. Such a preponderance of one sex is indeed striking; and yet an analysis of the cases throws no light upon the significance of this relative frequency of the condition in females. The features which tend toward the greater frequency of other diseases of the biliary passages, especially gallstones, in females are certainly not concerned in the production of cysts of the bile ducts, for these features are, for the most part, dependent upon modes of dress or functions peculiar to the female sex, possible only in adult life; and the majority of cases of cysts have occurred in the young. Of the 22 cases in which the age was mentioned, the average was fifteen years and eight months; 2 were under one year of age; 7 were between one and ten years of age; 6 between ten and twenty years of age; 4 between twenty and thirty; 1 between thirty and forty; and 2 between forty and fifty years.

Turning our attention to the anatomical peculiarities presented by the cases that have been studied, especially in regard to the lower end of the common duct and any condition existing there to cause obstruction, we find that of the 19 cases in which the result of this examination was mentioned, gallstones were found in 3, a papilloma in 1, myomyxomatous polyps in 1, scirrhous pancreatitis in 2, catarrhal cholangitis in 1, a simple stenosis or obliteration of the peripheral end of the lumen in 6, and a valve-like fold or angular insertion of the duodenal end of the duct in 5 cases. In addition, 2 of the cases in which the peripheral end of the duct was obliterated showed also this angular insertion. This great variety in the apparent cause of

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the obstruction and subsequent dilatation at once suggests that there is no unity of the pathogenesis of cysts of the bile ducts, but that any obstruction of the lower end of the duct may lead to cyst formation. However, let us conduct a further analysis. Of the 4 cases over twenty-one years of age in which the cause of the obstruction was mentioned, gallstones were found in 2, a papilloma in 1, and a valve-like fold in 1. Whereas, in the 13 cases under twenty-one years of age, a simple obliteration of the lumen was found in 6 instances, a valve-like fold in 4, catarrhal cholangitis in 1, and schirrhous pancreatitis in 2. I doubt the value of the opinion that scirrhous pancreatitis was the cause of the obstruction in the 2 cases so reported. They were both, observed many years ago—one in 1723, the other in 1817. Considering the degree of firmness presented by the normal pancreas to palpation, and realizing the infrequency of scirrhous pancreatitis in childhood, I am loath to accept this diagnosis unsupported by a histological examination.

In considering the cases in which an obliteration of the lower end of the duct was found, we can but conjecture what the cause of this obliteration may have been. The fact that practically all these cases occurred in early life might suggest that a congenital atresia of the bile ducts was at the basis of the condition, but this is extremely improbable, for the vast majority of infants suffering with congenital atresia of the bile ducts die before the eighth month of life.[1] The fact that the case reported by Rolleston showed many manifestations of congenital syphilis, and the probable history of syphilis in the father of the patient whose case I am reporting, naturally direct attention to the possibility of the obliteration being the result of a syphilitic fibrosis. However, in the other cases there is not sufficient basis for entertaining this opinion; and it must be considered as but a vague possibility. Another possibility is that the obliteration was the result of the organization consequent upon a catarrhal cholangitis. This hypothesis seems plausible in my own case, at least, by reason of the fact that symptoms of catarrhal cholangitis preceded for some time the development of the tumor; though, of course, it must be admitted that the latter may have been present a considerable period

[1] Lavenson, Jour. Med. Research, 1908, civ, 61.

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before it was recognized by the parents. Why the duct should undergo such extensive dilatation in the presence of an obstruction in early life, as compared with the infrequency of the same occurrence in the obstructions of later life, is difficult to explain. Probably the force with which the bile is excreted is not much less in early life than in adult life, but the more delicate walls of the bile ducts of the young are less able to withstand the strain of increased internal pressure. There must, however, be some element in addition to this; otherwise it would be rational to expect to find cysts in at least some of the cases of congenital obliteration of the bile ducts in which the obstruction is in the lower end of the duct; I am not aware of any such case having been reported. The other element in the production of the cysts is, in all probability, a congenital weakness of the muscular tissue of the wall of the duct.

In the cases of Douglas, Arnolds, Fenger, Arnison, Rostowzew, and Konitzky, and in my case, the lower end of the duct, or its fibrous remains, was found to enter the cyst at so acute an angle as to produce a valve-like formation at the duodenal end of the cyst. Rostowzew looks upon this angular insertion of the duct as the cause of the obstruction and the subsequent dilatation. His view can be best appreciated by glancing at the accompanying diagrams. As is shown in Fig. 3, the intramural portion of the common duct runs normally from left to right; in other words, in the same direction as the portion of the duct above the duodenum, but at a somewhat more acute angle. Rostowzew believes that in some cases the intramural portion of the duct, instead of running from left to right, runs from right to left, as is shown in Fig. 4. This, according to his view, produces a kink, which results in obstruction to the outflow of bile and subsequent cyst formation, as is shown in Fig. 5. I believe Rostowzew's hypothesis to be incorrect. In my opinion the angular insertion of the duct is the result of the cyst formation, and not its cause. If one recalls the anatomical relations of the common bile duct as it runs in the gastrohepatic omentum, it will be appreciated that lying farthermost to the right as it does, any tendency to dilatation that it may assume toward the left would have to overcome the resistance offered by the hepatic artery and the portal vein; whereas, to the right no structures are interposed to restrict its dilatation.

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In my case, in which, in addition to obliteration of the duodenal end of the duct, this angular insertion was found, it can be seen by glancing at the accompanying photograph of the cyst (Fig. 2) that the dilatation was entirely to the right. The short straight line *B*—*C* represents the left wall of the common duct, the right wall alone being distended to form the cyst. With such extensive dilatation

FIG. 3

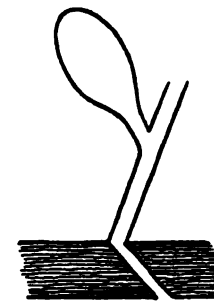

FIG. 4

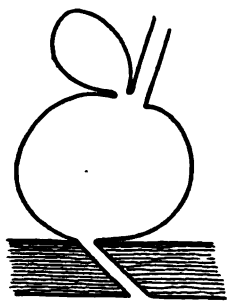

FIG. 5

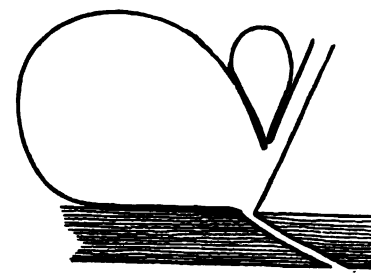

FIG. 6

FIGS. 3, 4, 5, and 6.—The varying modes of insertion of the common bile duct into the duodenum.

to the right, the peripheral undilated portion of the duct is compelled to change its direction, and instead of running from left to right, as it normally does, to run sharply from right to left, as is shown in Fig. 6.

This view is substantiated by the fact that in 3 of the 7 cases in which this angular insertion was present, obliteration or obstruction

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of the peripheral portion of the lumen was also found. In the other 4 cases it is not specifically mentioned whether or not the peripheral portion of the duct was patulous. Assuming that it was patulous, I believe it probable that in the presence of a congenital weakness of the muscular tissues of the duct wall a temporary obstruction, as by a catarrhal cholangitis or a mucous plug, could offer sufficient resistance to the outflow of bile to result in dilatation and a consequent angular insertion of the lower end of the duct. Even though the cause of the obstruction should subsequently subside, by the time the cyst is formed the valve-like opening could undoubtedly act as a secondary cause of obstruction.

SYMPTOMATOLOGY. There is little to be said of the symptomatology of the condition, aside from what has already been mentioned in discussing its pathology and pathogenesis. It should be recalled that in many of the cases symptoms of biliary obstruction have preceded the formation of a cyst, or, probably better, the recognition of a cyst, by a considerable period of time. Recognition must also be taken of the fact that it occurs relatively much more frequently in childhood and in the female sex. The conditions with which it is most likely to be confused are cysts of the pancreas and dilatation of the gall-bladder. Probably, in the vast majority of cases, only an exploratory incision will determine the diagnosis.

TREATMENT. It can be readily appreciated that surgery offers the only possibility of cure. Of the 21 cases in which more or less extensive surgical procedures were adopted, simple puncture of the cyst was performed in 3 cases, all of which resulted in death. Incision and drainage was performed in 14 cases, with 13 deaths. Cholecystenterostomy was performed in 4 cases, with 3 recoveries. The latter operation thus seems to offer the best chances of cure.

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1908.

The Human Spleen as a Hematoplastic Organ, as Exemplified in a Case of Splenomegaly with Sclerosis of the Bone Marrow.

By J. L. DONHAUSER, M.D.

(From the Ayer Clinical Laboratory, Pennsylvania Hospital.)

THIS paper has been written for the following reasons:

1. To present a case of splenomegaly with very unusual pathological findings.

2. To show the similarity which may exist between bone-marrow changes and splenic transformation, and the relation of the one to the other.

3. To consider certain types of splenomegaly as being compensatory processes dependent upon and due to bone-marrow disease.

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HISTORY OF THE CASE. The patient, Samuel K., an oiler, aged fifty-eight years, was brought to the Pennsylvania Hospital, August 5, 1907, in the ambulance during the service of Dr. J. C. Wilson, whom I wish to thank for the following notes:

He complained of malaise, weakness, dyspnea, shortness of breath, insomnia, loss of appetite, nausea, constipation, and edema of the lower extremities. His father died of "debility;" his mother, as result of an accident. Three brothers and two sisters are dead, the causes unknown. Three brothers and three sisters are living and well. There has been no chronic illness in the family. The patient was born in County Dongon, Ireland. He lived there until he was thirteen years old; he came to the United States when fourteen, worked on a farm for three years, and then was employed by the Traction Company as driver and conductor for twenty-three years. He was employed as "workman on road" up to 1902. Since then he has done odd jobs. During the last two years he has been employed as an oiler in an engine room. He has always been a healthy individual. He had measles, mumps, and whooping-cough when a child. Patient states that so far as he knows he has never been sick before the present illness (with the exception of diseases of childhood). There is no history of malaria, syphilis, or gonorrhea. He drinks a fair amount of tea and coffee. He occasionally drinks whiskey and gin, as well as considerable beer—fifteen to twenty glasses a day. He has taken no liquor for past three years.

Patient thinks that his illness began about the first of June, 1907, with a swelling of the lower extremities, dyspnea, and shortness of breath, which gradually increased; he was unable to sleep or lie down with any degree of comfort. Appetite was poor; he was nauseated, and vomited once or twice; bowels were regular; there was no cough or pains in chest. There was occasionally slight vertigo. There was no abdominal pain, distention, or tenderness. Patient worked until the middle of June, when he was compelled to stop, as his condition was becoming worse. He went home and remained there, but did not go to bed. Symptoms gradually became more marked; his feet and legs became more edematous, dyspnea and shortness of breath increasing, with slight precordial pain; appetite became poorer. He began to notice that the abdomen and

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scrotum were becoming swollen. He was unable of late to lie down on account of dyspnea. Sleep was very poor. On admission to the hospital temperature was 99° F.; pulse, 108; and respirations, 36.

Physical examination shows a fairly well-developed though emaciated man, past middle age. He sits up in bed and is unable to lie down. He breathes with difficulty and is bloated and anemic. Abdomen and extremities are moderately swollen and edematous, and pit on pressure. Pupils are equal and react to light and accommodation. Conjunctivæ are clear though anemic. The tongue is moderately coated, moist, and not tremulous; the breath is offensive. There are some pulsations of vessels of neck. There are no enlarged glands; no rigidity. Brownish pigmentation is present at the root of the neck. Chest is fairly well developed and symmetrical; expansion is poor. At the base of both lungs there are some crepitant and mucous rales, with slight impairment to percussion; breath sounds are somewhat suppressed and distant, but otherwise the lungs are clear. There is normal vesicular breathing, with no impairment of resonance; vocal fremitus is fair.

The area of cardiac dulness is slightly enlarged, extending to the upper border of the third rib and 3 cm. to the right of the midline; the heart beat is circumscribed and moderately forcible. There is also seen and felt just at the edge of costal margin, 1.5 cm. to left of the midline, an impulse. Heart sounds are heard fairly well at all the cardiac areas; they are somewhat forcible, but not clear and distinct, and seem to lack muscular tone. At the apex there is heard, at times, a soft systolic murmur transmitted to the base. The pulse is moderately rapid, fairly soft and compressible, and at times slightly irregular. The arteries are slightly sclerotic. The abdomen is quite distended and tense, and pits on pressure in the lower quadrants. On percussion there is dulness in the flanks, and the lower quadrants are slightly tympanitic below costal angle; there are definite succussion splash and movable dulness. There is a large mass in left upper and lower quadrants, apparently projecting from below the costal margin. It is quite hard, apparently solid and smooth, and tender to palpation. The mass extends from the costal margin into the pelvis, approximately measuring 23 cm. and from the median line to left flank, 23 cm. It does not move with respiration, and moves only slightly on

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change of position. Coils of intestine can be felt floating over the mass. Liver reaches from the fourth rib in midclavicular line to the costal margin, and is tender on palpation. There is no pulsation. The mass in the left quadrant is apparently the spleen, or else is fused with it. Pelvis and scrotum are somewhat swollen and edematous. There is moderate edema of the lower extremities.

On admission the hemoglobin was 85 per cent. (Dare). The blood count was as follows:

Leukocytes	11,550 per cu.mm.
Polymorphonuclear leukocytes	71.6 per cent.
Large mononuclear leukocytes	13.2 "
Small mononuclear leukocytes	8.4 "
Transitional leukocytes	6.0 "
Eosinophile leukocytes	0.4 "
Basophile leukocytes	0.4 "

Urine is reddish yellow, acid, sp. gr. 1023; there is a large amount of albumin; no sugar; hyaline and granular casts, a few leukocytes, epithelial cells, and mucous cell detritus are found.

Patient improved for a time, but gradually became worse and died of asthenia September 10, 1907. After the first day the temperature never advanced above the normal point.

The blood was examined from time to time while the patient was in the hospital, but apart from the fact that there were evidences of a gradual decrease in the hemoglobin, a slight decrease in the number of red blood corpuscles, and a moderate increase in the large mononuclears, the blood picture showed nothing unusual. The lowest percentage of hemoglobin was 50 per cent.; the minimum number of red blood cells, 3,220,000; of white blood cells, 8950. The differential counts were suggestive of nothing. At no time in the course of the disease were nucleated red blood cells found.

An autopsy was performed seven and one-half hours after death. The report is as follows:

The body is that of a well-built, rather poorly nourished adult male, measuring 155 cm. in length. Rigor mortis is present to a slight degree. Bluish-red discoloration of dependent parts. Pupils are equal, clear, and widely dilated. No lymph glands palpable. External genitalia apparently normal. The abdomen is protuberant.

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Abdominal cavity contains approximately 500 c.c. of a clear straw-colored fluid. The bowels are in a collapsed condition and the omental fat is scanty. The parietal and visceral peritoneal surfaces are smooth and glistening, with well-injected vessels. The mesenteric glands are enlarged. The appendix is directed downward, inward, and upward in the right iliac fossa; it measures 5 cm. in length, is patent throughout, and apparently normal. The spleen is seen to extend 5 cm. below the costal margin.

Each pleural cavity contains approximately 1000 c.c. of a yellowish brown, clear fluid. There are a few adhesions over the right pleura; the left lung is bound to the chest wall by numerous adhesions. The pericardial cavity contains about 50 c.c. of a clear straw-colored fluid. The visceral pericardium is covered, in numerous areas, by large white plaques which are firmly adherent to the underlying tissue.

Heart. Weight, 450 grams. The right ventricular wall measures 8 mm. in thickness, the left ventricular wall 3.25 cm. in thickness. The heart's flesh is of a pale red color, very firm in consistency, and there is evidence of an increase in the interstitial connective tissue. The coronary arteries are patent throughout and free from sclerosis. Tricuspid, aortic, and pulmonic valves are negative. The anterior leaflet of the mitral valve is somewhat hard in consistency and apparently slightly thickened. Five millimeters above one of the aortic cusps is a calcareous area measuring 1 cm. in diameter.

Lungs. The right lung is voluminous, crepitant in some portions, and boggy in other areas. It is of a purple color. No nodules are felt. On section a gray fluid exudes from a cut surface, which is of a gray black color dotted with small areas of a dark red. A few white fibrous plaques are found in the right pulmonary artery. The left lung is somewhat smaller than the right one and is tougher to the feel. The external surface is purplish gray in color. On section the upper lobe resembles the right lung. The lower lobe is, however, entirely collapsed, and is of a dark red brown color; on pressure it exudes a slight amount of frothy red fluid. There are a few sclerotic patches in the left pulmonary artery.

Mesenteric glands are greatly enlarged throughout and on section present areas of caseation and calcification.

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Spleen. 22 x 15 x 8.5 cm.; weight, 1470 grams. Its external surface is covered with small and large fibrous tags. The organ is very firm and regular to the feel. Small whitish plaques, varying in size from that of a millet seed to a split pea, are noted over its entire surface. On cut section the capsule is seen to be somewhat thickened, and the organ, as a whole, of a dark red color. The trabeculæ are very distinct. The Malpighian bodies are barely visible. Scattered throughout and indiscriminately arranged are small, rather soft areas of a light red color, spherical in form, varying in size from a pin point to that of a large bean. These soft nodules stand out prominently as light red areas in contradistinction to the surrounding tissue, which is of a much darker red. The above-described portions do not appear to be encapsulated, though they are definitely spherical.

Kidneys. The right kidney measures 8 x 6.5 x 4 cm. The capsule strips quite readily, though it is slightly adherent in areas. A small retention cyst is noted. On section the cut surface is gray red in color. The cortex measures 8.5 mm. in thickness. The glomeruli are rather prominent; the pyramids and striæ very distinct. The pelvic fat is normal in amount.

The left kidney measures 10 x 4.5 x 3 cm. It is somewhat lobulated and rather soft in consistency. The capsule strips with difficulty. On section the cut surface is gray red in color. There is evidence of confluency of cortex with the pyramids, no distinct line of demarcation being seen. The glomeruli are quite distinct, as are also the striæ and pyramids. There is a small cortical retention cyst.

Liver. 23 x 12 x 9 cm.; weight 2130 grams. It is very hard to the feel. The external surface is free from adhesions and is of a pink gray color. The edges are slightly rounded. On section the cut surface is reddish yellow in color, studded with small patches of yellow red, especially noted toward the centre of the liver lobules. There is a marked engorgement of the capillaries. The portal connective tissue is apparently slightly increased in amount. The bile ducts are patent; no stones are found. Vessels are apparently normal.

Gall-bladder contains approximately 50 c.c. of a viscid brown fluid.

Adrenals are apparently normal.

Urinary bladder is apparently normal.

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Testicles are somewhat edematous, but there are no signs of orchitis. There is a small cystic tumor of the right epididymis.

Prostate and seminal vesicles are apparently normal.

Aorta is apparently normal.

Gastric mucosa shows congestion, and is covered with thick mucus; otherwise it appears normal.

Pancreas is apparently normal.

The intestinal mucosa, especially in the neighborhood of the big gut, shows a marked hyperplasia and is covered by thick mucus, such as is seen in the stomach. In the neighborhood of the jejunum there is marked vascular injection.

Bone marrow removed from the middle portion of the right femur shows a very firm dark brown red tissue.

Anatomical Diagnosis. Acute edema of lungs. Dilatation and hypertrophy of right and left ventricles. Chronic myocarditis. Chronic splenic tumor. Atelectasis of lower lobe of right lung. Chronic parenchymatous nephritis. Cloudy swelling of the liver and kidneys. Tuberculosis of mesenteric lymph glands. Sclerosis of bone marrow. Fibrinous pleurisy.

Microscopic Examination. Heart: Muscle fibers are of normal size, but are quite granular and contain a fair number of vacuoles. There is some increase in the interfibrillar connective tissue.

Lung: Pleura is somewhat thickened. Many of alveoli are filled with a serous-like material. Capillaries are engorged; no large giant cells are seen.

Liver: Capsule shows moderate thickening. The liver cells are swollen and granular and show a well-advanced grade of vacuolization. Some areas show so high a degree of granulation that the liver cords have completely lost their contour and appear piled upon one another. Extending from the centre of many of the lobules, and in some portions almost to the periphery, are areas of necrosis with complete disappearance of the liver parenchyma; they have been filled with red blood corpuscles, vast numbers of polymorphonuclear leukocytes, and an occasional round cell. The connective tissue around the bile ducts shows slight thickening with round-cell infiltration. The periportal connective tissue is somewhat increased. The interlobular and intralobular connective tissue does not appear to be increased in amount.

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The bloodvessels and capillaries are filled with red blood cells. Their walls are normal. No multinucleated or large vesicular cells are found in any sections.

Kidneys: Attached to the cortex are bands of connective tissue which show a moderate degree of round-cell infiltration. At the juncture of the cortex with these fibrous bands are large clusters of round cells. Many of the glomeruli appear normal in all respects, others are atrophied, and still others have undergone a complete hyaline change. The epithelium of the tubules is swollen and granular, and many of the lumina are almost occluded by the swollen and desquamated cells. There is a slight increase in the intertubular connective tissue. The bloodvessel walls are slightly thickened. The capillaries and larger vessels are filled with red blood cells. No multinuclear or large vesicular nucleated cells are found.

Pancreas: The gland is apparently normal.

Mesenteric Lymph Glands: Capsule shows moderate thickening with extensive round-cell infiltration. The sinuses are in areas entirely obliterated by the proliferative and desquamative endothelial cells of the lymph spaces. Many of the lymphoid follicles have been entirely replaced by a necrotic tissue surrounded and infiltrated by large epithelioid, round cells and giant cells of the bipolar and mural type. Scattered within the tissue are polymorphonuclear leukocytes, especially seen around the areas of necrosis. Many of the germinal follicles seem to be the starting point for the tuberculous process. No bone marrow giant cells or vesicular nucleated cells (except the epithelioid cells) are seen.

Bone Marrow: There is an enormous hyperplasia of the cellular and connective tissue elements. The types of cells seen are of all the varieties seen in the bone marrow under normal conditions. Thus, the types seen are neutrophilic and eosinophilic myelocytes, polynuclear leukocytes, giant cells, large and small mononuclear cells, normocytes, normoblasts, and megaloblasts, together with large numbers of fibroblasts of the connective tissue. The cells, as a whole, lie embedded in a very much thickened and well-formed connective tissue membrane containing well-developed bloodvessels and capillaries (Mallory's connective tissue stain). The neutrophilic myelocytes are for the most part arranged in clusters, and are occasionally

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seen bunched together in spaces lined with endothelium. The cells described as myelocytes are the fairly large mononuclear cells which appear to contain neutrophilic and eosinophilic granules; no true basophilic myelocytes are seen. Scattered indiscriminately throughout the tissue are large giant cells which appear in two forms (though their nuclei, which often contain a nucleolus, and their nuclear fibrillar network, together with their hyaline appearing protoplasm, are the same): one type of cell possesses numerous nuclei, arranged generally in the centre, and is composed of large vesicular nuclei and nucleoli with a well-defined network and surrounded by a hyaline appearing protoplasm. To this type is applied the term polykaryocyte; the other type, or megokaryocyte, possesses but one singular lobulated nuclear cast, possessing a nucleolus, well-defined nuclear membrane, and surrounded by a large amount of hyaline appearing protoplasm. Throughout the section are noted enormous numbers of very large cells with vesicular nucleus, about which is a small, apparently non-granular, rim of protoplasm, which has a tendency toward taking the alkaline stain. These cells contain often a well-developed nucleolus. They have a tendency toward cluster arrangement, and some definite masses of these cells are seen in spaces lined by endothelial cells. Arranged among erythrocytes and also scattered indiscriminately among the other cells are fairly large numbers of normoblasts, some of whose nuclei are in the process of extrusion. An occasional megaloblast with dividing nucleus may be seen. The polynuclear cells are scarce as compared with those of normal bone marrow, though here and there some are noted. They have no tendency toward arrangement in clutsers. There are definite large masses of small mononuclear cells or lymphocytes seen in different portions of the sections. An occasional polynuclear eosinophile with no definite position is seen. Coursing everywhere are enormous numbers of fibroblasts and larger and more developed connective-tissue cells. The blood-vessels are large and well developed, with thickened walls. The capillaries are markedly increased also. There are no organisms seen in sections. A noticeable feature is the presence of very large numbers of small mononuclear cells and fibroblasts, with a relative decrease in the normal functionatory marrow cells.

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Spleen: Capsule is somewhat thickened, is infiltrated with round cells, and has attached to it small and large strands of connective tissue. The trabeculæ and bloodvessels show a slight hyperplasia; there is a marked increase in the reticulum. Many of the Malpighian bodies appear intact, though the majority of them show some atrophy, many of them having disappeared. The splenic pulp is markedly hypertrophied, and is found to contain large clusters of well-formed and well-preserved red blood corpuscles. Scattered here and there among the pulp cells are seen very large cells with vesicular nuclei, some cells containing but a rim of a homogeneous protoplasm, while in others the protoplasm is more extensive and apparently contains what are perhaps neutrophilic granules. There is a marked tendency on the part of these cells to cluster together and lie within spaces lined by epithelial cells. An occasional multinucleated giant cell of the bone marrow type is seen; many normoblasts are visible. There is an extraordinarily small amount of pigment.

Splenic Nodes: Surrounded by a tissue which microscopically resembles the above, are areas from 1 to 2 cm. in diameter, which greatly differ in some respects from the surrounding tissue. These areas are made up almost entirely of large cells, containing a vesicular nucleus and but a rim of protoplasm. They are for the most part in small spaces, some of which appear to be lined with endothelial cells. Bone marrow giant cells, both of the multinuclear and polynuclear forms, are present in abundance. All these cells are supported by a connective-tissue meshwork, which contains also large numbers of nucleated red cells and erythrocytes arranged in no particular fashion. No pigment is seen.

Microscopic Diagnosis: Edema and congestion of lungs. Fibrinous pleurisy. Chronic interstitial myocarditis. Fatty metamorphosis of heart and liver. Chronic splenic tumor, with bone marrow cell hyperplasia. Cloudy swelling of heart, liver, and kidneys. Chronic diffuse nephritis. Primary tuberculosis of mesenteric lymph nodes. Sclerosis of bone marrow.

As the term splenomegaly is now applied it has especial reference to a splenic hypertrophy which has extended over a period of months, perhaps years. Some writers include under the word splenomegaly only those conditions in which there is an idiopathic enlargement of

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the spleen, accompanied by an anemia or perhaps an anemia with a cirrhotic liver. Others apply the term to a condition in which there is an enlarged spleen with known or unknown etiology. The causes of many of the splenomegalies are still so uncertain that to formulate any definite classification from an etiological standpoint is wholly impossible. It is not the purpose of this report to discuss all of the various conditions which may give rise to an enlarged spleen. The main interest arises as to the etiology of these cases grouped under the term "splenic anemia." At the present time their origin is attributed to some intoxication, chronic in form, which principally affects the spleen, though sclerosis of the splenic and portal vessels and thrombosis of the splenic sinuses have been given as possible causative agents. That a diseased bone marrow might be the contributing cause in some of the cases has not been suggested, and it is important, therefore, to present an example in which the bone marrow is as extensively affected as the spleen.

This appears to be the condition in the case just described. What toxin, if any, caused the chronic inflammation of the bone marrow in this case is not known. It should be remembered, too, that from the histological examination the bone marrow presents a more intense and perhaps more advanced sclerosis than does the spleen, and that the greater part of the bone marrow elements, as seen in the sections, are not the true blood-forming cells of the body, but are principally lymphoid cells and fibroblasts. Associated with this intense sclerosis of the bone marrow are the definite foci composed of true bone marrow elements in the spleen.

It is needless to add that a differential diagnosis from the other splenomegalies is not necessary. From a review of the literature it has been seen that the case described above does not resemble the types heretofore reported.

The pathological changes which take place in the various forms of splenomegaly, particularly of the primary type, are not uniform, and the relative bearing of the bone marrow upon cases of splenomegaly has been but briefly commented upon. It is, therefore, only by careful examination of individual cases and by experimentation upon animals that we may hope to arrive, some day, at conclusions as regards the physiological and pathological properties of the splenic hypertrophies.

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In consideration of all cases of enlarged spleen, especially when the etiology is entirely unknown, we must of necessity turn to the so-called hemopoietic organs, in which group are included, besides the spleen, the bone marrow, lymph glands, liver, and hemolymph glands. That a decided relationship exists between the first three has been proved by all who have spent much time in study of the subject. The liver too undoubtedly plays an important role, while Warthin's[1] work on the *Anatomy and Physiology of the Hemolymph glands*, together with W. B. Drummond's[2] monograph on the same subject, have brought these structures into an important relationship with the other tissues considered as exciting some special action on the blood's function or destruction. Bizzozero and Neuman long ago demonstrated the fact that the bone marrow was the seat of formation of the red blood cells. Soon after, Ehrlich not only verified this statement, but also demonstrated that the bone marrow was the site of white-cell formation. Investigators of later date have found these facts to be true, and we are now in the position to give the most important functions of the bone marrow. The function of the lymph gland cannot be asserted as definitely, but the fact remains that the lymph glands cannot be excluded from those organs described as being hemopoietic. They are possibly the place of origin of the lymphocytes of the circulating blood, and from chemical and experimental observations it appears that they have power to assume, at some time, perhaps a compensatory function. The liver in embryonal life aids in the blood's formation, while as age advances it gradually loses that power and helps in the carrying off of waste matter, the result of disintegration of red cells. The functions of the hemolymph glands are still in dispute; thus Drummond[2] claims that "there is no sufficient evidence that the hemolymph glands play any part in the formation of red blood cells, but that, on the other hand, they appear to perform a very active part in the destruction of red blood cells and in the liberation of pigment." On the other hand, Warthin[1] says that "the close relation between spleen, lymph glands, and bone marrow is shown by the power of the hemolymph glands to take on a structure of either spleen or marrow and to compensate for these organs when their function is abridged by disease." And finally, the spleen has perhaps caused more discussion than any of the other organs. Dif-

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ferences in the cellular contents and structural characters in various animals have proved a barrier for decisive experimental work. Thus, in lower vertebrates and in some of the mammalia, as the mouse, hedgehog, and rabbit, nucleated red cells are normally present, giving evidence of a formation of red blood cells in the spleen. Ehrlich,[3] on the other hand, states that in the human spleen nucleated red blood cells are not to be found normally. Other investigators do not substantiate this phase of Ehrlich's work, and claim that under normal conditions normoblasts are often found in the human splenic pulp. It is for this reason extremely difficult in animal experiments to determine the part taken by the spleen in forming erythrocytes. It is generally believed that though the spleen may be one of the sources of origin of red blood cells, its main duty is the absorption of the material due to disintegration of red and white cells and to preserve a portion of it, at least, for the organism.

The main point of interest which concerns us is the significance that may be attached to a pathological change in the spleen in which we see definite bone marrow elements, including giant cells arranged in isolated areas through the splenic pulp. The presence of giant cells, resembling in all respects those of the bone marrow existing in the human spleen, has been mentioned and but slightly commented upon by Dock and Warthin,[4] Rolleston,[5] and Simonds.[6] Dock and Warthin interpret them as being emboli, while Rolleston and Simonds offer no hypothesis. On the other hand, numerous investigators, such as Dominici, Opie, Jarotsky, Bunting, and others have commented upon their presence in the hedgehog, the rabbit, and the guinea-pig, under normal as well as under pathological conditions. Under all normal conditions bone marrow giant cells are absent from the human spleen and they appear only during an acute or chronic intoxication. I have not been able to find a note on their presence in the acute infections of human beings, though in one case which I have studied, the spleen from a patient dying with acute gonorrheal endocarditis showed definite bone marrow cells, including the true myeloplaxes and the large granuleless mononuclears arranged in small clumps. Dock and Warthin's report on the pathology of two cases of "splenic anemia" is interesting, since in one of their cases giant cells resembling those of the bone marrow were found in great

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numbers in the lung capillaries, while a smaller number were found in the liver capillaries and blood spaces of the spleen and hemolymph glands. In the other case there were found large numbers of these cells in the lungs, a smaller number in the spleen, and a fair number in the hemolymph glands. In both cases there was a decided decrease of giant cells in the bone marrow. As stated above, the writers considered these cells emboli.

The question now arises whether there are splenomegalies in which the bone marrow's function has become exhausted by the action of some circulating toxin and in which the spleen exerts itself in a compensatory manner by forming new blood elements for the organism.

Osler, Sippey,[7] and Simonds[6] have thoroughly reviewed the literature of splenomegaly, and hence the citation of cases will be dwelt upon only so far as it may have a definite bearing on the subject under discussion. The cases of so-called "splenic anemia" or splenic anemia with cirrhosis of the liver (Banti's disease) form the greater part of the cases of obscure origin. In these the pathology has been quite well outlined by Rolleston,[5] who says that the main pathological changes in splenic anemia are: (1) Fibrosis of the organ, (2) atrophy of the lymphoid elements, and (3) fibrosis of the Malpighian bodies. In addition there is usually no evidence of exaggerated hemolysis such as excessive pigmentation of the spleen. He notes also that there is usually a red marrow transformation, though the yellow marrow may persist.

The pathological changes seen in the present case are entirely different from those which have been described previously. Macroscopically distinct, small, rather soft areas, of a light red color, spherical in form, varying in size from a pin-head to that of a large bean, were quite striking. Simonds[6] describes an enlarged spleen as containing "numerous round, oval, or branched reddish brown areas about two millimeters in diameter." In this case the areas, containing a large amount of pigment, gave an intense iron reaction. The difference is obvious, since the areas described in my case are free from pigment and are seen to be made up of collections of what appear to be definite bone marrow cells. There was great similarity between sections of the bone marrow and sections through these areas in the spleen. For a comparative study of the bone marrow and the cells in the nodules

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the most useful stains were Duval's modification of Leishman and Wright stains, polychrome methylene blue, hematoxylin and eosin, Mallory's connective-tissue stain, Van Giesen's stains, and Ehrlich's triacid stain. With none of these stains, however, have definite neutrophilic granules been made out in the cells, either in the spleen or bone marrow. This is perhaps due to the fixation which unfortunately was entirely in Zenker's fluid. Some of the cells of the bone marrow presented what appeared to be neutrophilic granules. There were cells in the spleen which had the same appearance, but I cannot state positively whether they were or were not myelocytes. It can be definitely said, however, that the giant cells, the megakaryocytes, were present in both tissues and that the large granuleless mononuclear cells found normally in the bone marrow alone were present in great abundance in these nodules in the spleen.

The question now arises whether this enlargement of the spleen should be considered as a heteroplastic growth or as a hyperplastic. We meet with three hypotheses: (1) That the condition is due to a disease of the spleen *per se;* (2) that the bone marrow foci found in the spleen are emboli and the enlargement is due to an intense congestion; (3) that the enlargement depends upon the spleen assuming a dormant hemopoietic function with hyperplasia of the cells of the spleen pulp.

The determination as to whether the condition was primary in the spleen in this case is impossible. From the examination of the bone marrow, it seems more probable that the sclerosis there is of an older form and of a greater intensity than it is in the splenic pulp. The theory that these masses of bone marrow tissue arise from bone marrow cell emboli cannot hastily be disposed of, for the two cases reported by Dock and Warthin, referred to above, which showed definite bone marrow cells in the capillaries of the liver, spleen, hemolymph glands, and lungs, together with Bunting's[10] report of the finding of definite bone marrow in the dorsal portion of the aorta, would perhaps suggest the possibility of such an emigration of cells. Bunting, however, states that one is not justified in deciding whether they were formed by a further metaplasia of connective-tissue cells or by a metaplasia of emigrated cells from the blood stream, capable of differentiation into the various types of marrow cells. In my case it does not seem

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probable that the bone marrow elements have been brought to the spleen by the blood stream, for if such were the case it would seem reasonable to suppose that these same cells should be found in the lungs and liver, as in the two cases of Dock and Warthin. On the other hand, possibly such a process cannot be entirely ruled out, for the clusters of marrow cells, some of which are found in blood spaces, suggest at least the idea that they may be emboli. However, from a careful study of the sections as regards the position of the bone-marrow cells and the condition of the lymph nodes, liver, and lungs, I do not feel justified in stating that they are brought directly to the spleen from the bone marrow.

Finally, we come to the third proposition, as to whether the enlargement may be due to the development within the spleen of blood-forming elements. This hypothesis really rests upon two conditions, namely: (1) That the bone marrow cells are fetal remains of cells which have been lying latent, and through a stimulant, perhaps exciting the bone marrow to activity and finally to uselessness, have increased in proportion and have taken on their original fetal blood-forming function; (2) that the spleen has produced bone marrow cells from the blood or lymph spaces. Before arriving at any conclusion whatsoever as regards the logic of either of these two hypotheses, it is necessary to consider the subject, as best we can, from an experimental standpoint, for it is only by this means that we may throw some light on the subject. Indeed, from the sections of organs removed at autopsy no consecutive changes can be noted.

It is an accepted fact that the human and mammalian fetal spleens contain a varying number of bone marrow cells, such as the giant and myelocytic cell, together with large numbers of nucleated red blood corpuscles. As the human spleen becomes further developed the bone marrow and normoblastic cells gradually disappear, while in the spleens of many of the mammals the blood foci cells persist through life though in greatly decreased numbers.

Experiments of Pugliese[11] on hedgehogs have shown that after repeated bloodlettings the giant cells increase markedly in the spleen, and that after partial splenectomy the giant cells in the intact splenic tissue show a decided increase; that with total extirpation of the

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spleen the bone marrow becomes filled with giant cells, and that after repeated venesections the giant cells increase in the spleen but remain unchanged in bone marrow, whereas in the liver and lymph glands there are no traces of them. The experimental anemias produced by Bunting[12] in rabbits throw much light on the compensatory power of the spleen. Thus, after sclerosis of the bone marrow had been produced the spleen showed a marked dilatation of the peripheral venous sinuses which were crowded with marrow cells, and especially numerous were the megakaryocytes. Myer and Heinecke[13] have shown similar changes in the spleen in a case of pernicious anemia. Bunting[12] comments upon the fact that bone marrow, following injection of hemolytic toxins, becomes sclerotic and there may be an almost entire replacement of the hemopoietic elements by the newly formed connective tissue, while hemorrhages cause only the hyperplastic marrow of a secondary anemia. Clinically it has been noticed that an enlargement of the spleen often causes an improvement in the general condition of the blood.

Dominice[14] has subjected rabbits to repeated bleedings, and has found practically the same histological changes in the spleen as has Bunting. He has observed, however, that in the course of experimental infections with the typhoid bacillus there takes place what may be called "a partial myeloid change." By this term Dominice means that all the elements of the bone marrow are not present. Thus, there are noted large normoblasts and basophilic and neutrophilic myelocytes, but the eosinophilic myelocytes and giant cells are very rare or entirely absent. Jarotsky's[15] experiments with white mice infected with the hog cholera bacillus further substantiates the findings of Bunting, Pugliese, Dominice, and others. Jarotsky produced in twenty-four hours an enormous increase of giant cells and myelocytes in the spleen.

Opie[19] has observed the occurrence of eosinophilic myelocytes and bone marrow giant cells in the spleens of guinea-pigs four hours after inoculation with Bacillus pyocyaneus, Bacillus anthracis, and Bacillus mucosus capsulatus; he believes that these elements are derived from the bone marrow and are not formed in the spleen.

With the exception of some of Bunting's work on the experimental

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anemias, investigations of the subject have been limited to the acute infections. It is indeed fortunate that cases have been recorded in which similar splenic changes have taken place in the course of what appears in the present state of our knowledge to be a condition of chronic intoxication or infection, namely, pernicious anemia. Careful histological study of 17 cases of pernicious anemia by Gulland and Goodall[16] shows that in 8 of the 17 cases cells like those of the bone marrow were found in the liver, while in 4 cases myelocytes were found in the spleen, and in 1 case there were typical large bone marrow giant cells in the spleen.

Dominice and Jarotsky have written at length upon the possible mode of origin of the bone marrow cells in the spleen. Their findings, though interesting, are not at all convincing. The theories of transportation of bone marrow cell to the various organs can be substantially upheld by anatomical evidence in the leukemias. That the phenomenon takes place, however, in all cases where cells resembling those of the bone marrow are found in the various organs cannot be supported. On the other hand, experimental and anatomical evidence goes to substantiate, if not prove, the theory that the spleen under certain conditions of chronic inflammation of the bone marrow may take up the hemopoietic function. What the toxin is cannot be proved in many cases; but whatever the chemical changes may be, the toxin must have some deleterious effect upon the bone marrow, either prohibiting the growth of cells or so stimulating them as to finally exhaust their power to produce blood cells. It is but natural to suppose that the spleen lying dormant, as it were, in the body should at times be called upon to perform or at least aid in performing the activities of the marrow.

Conclusions. 1. The nodules found in the spleen are islands of active hematoplastic tissue.

2. The bone marrow, at least in the case which has been described, has been the primary focus of disease; some toxin has probably produced a chronic inflammatory change.

3. The bone marrow, owing to its enormous sclerosis, has lost its hemopoietic powers totally or to a marked degree, and the spleen has reverted to its fetal power to form blood.

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March 12, 1908.

The Presence of Tubercle Bacilli in the Circulating Blood in Tuberculosis.

BY RANDLE C. ROSENBERGER, M.D.

THE principal reason for taking up a bacteriological study of the blood in tuberculosis was to determine whether a previous assertion, made in connection with my article on the presence of tubercle bacilli in the feces, was correct. This assertion was that, considering the entrance of the tubercle bacillus into the human economy, "the number of bacilli is not large, and they find their way to the blood and lymph stream; and during their transit some are discharged through the feces and others through the urine." Again, after examination of the contents of twenty-two thoracic ducts from those dying of tuberculosis, tubercle bacilli were encountered in 72.7 per cent. This occurrence also led me to believe that all forms of tuberculosis were characterized by a bacteriemia.

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Some observers have been successful in obtaining cultures of the tubercle bacillus from the blood in cases of acute miliary tuberculosis, but the instances are not numerous.

The studies undertaken by me were at first to prove that tubercle bacilli were present in the blood in all cases of tuberculosis, and to determine if possible the presence of organisms in the so-called mixed infections in the late stages of the disease.

Numerous clinicians have asserted that the termination of cases of pulmonary tuberculosis was accompanied by infections of the pneumococcus, Streptococcus pyogenes, staphylococci, and Bacillus pneumoniæ. My own observations from examinations of the blood previous to the present study were usually negative as regards these mixed infections, as I never obtained any other organism besides the staphylococcus in quite a number of cases, even in those of tuberculous pneumonia. The occurrence of the staphylococcus was not considered as a possible infecting organism, but was usually looked upon as a contaminating organism from the skin.

In making up my list of cases for this research I first selected those who were bedfast and who presented advanced tuberculosis or cavity formation; then cases of acute miliary tuberculosis, and lastly, instances of incipient tuberculosis were studied.

The technique for the demonstration of tubercle bacilli in the blood was as follows:

About 5 c.c. of blood are withdrawn from a vein of the arm, and this is immediately placed in an equal quantity of a 2 per cent. solution of citrate of sodium in normal salt solution. The mixture is well shaken and placed in the refrigerator for twenty-four hours. At the end of this time there is an abundant sediment with the citrate solution slightly turbid. Centrifugalization immediately after mixing did not give very good results, so I determined upon letting it stand for twenty-four hours. After this time I pipetted off a quantity of the sediment, made a rather thick preparation upon a new clean glass slide, dried it upon a copper plate with moderate heat, and then placed it in distilled water until complete laking of the blood resulted. At this time only a delicate film remained. This was dried and fixed through a Bunsen flame and then stained by the usual technique for tubercle bacilli. As a rule, bacilli possessing the morphological and tinctorial

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properties of the tubercle bacillus could be demonstrated in the first slide thus prepared, though in several cases three slides were thoroughly searched before any bacilli were found. At least thirty minutes of careful searching should be done before a negative result is announced.

The pipettes before being used were thoroughly washed in water, then placed in pure nitric acid, and after being used were again washed, this time in a solution of caustic soda, rinsed, and again placed in pure nitric acid until ready for use. No one pipette was used on two different cases on the same day. Lately I have sterilized the pipettes at 160° C. for one hour, and then placed them in nitric acid before using. The syringes used for withdrawing the blood, as well as the needles, were boiled for about twenty minutes before and after using in a solution of caustic soda. The needles were kept in a solution of equal parts of lysol and glycerin, and just before use were washed in sterile water. The glass piston of the syringe, as well as the nozzle, was anointed with glycerin, to prevent any undue adhesion of these parts. No special preparation of the patient's arm is necessary, as lysol was simply applied upon the area as Wright practises in his opsonic work.

In the first few studies undertaken 10 c.c. of blood were withdrawn, then 5 c.c., and where for some unforeseen circumstance this amount could not be obtained from the patient 2 c.c. were taken. I would recommend 5 c.c. as the proper quantity to withdraw. Intimate mixing must be made lest the blood should clot, in which case the greatest difficulty arises in demonstrating the organisms.

The cases studied up to the present time number 50. Of these, 5 were diagnosticated as acute miliary tuberculosis; 2 as fibroid tuberculosis; 1 as pneumothorax; 15 as incipient tuberculosis; 23 as moderately advanced tuberculosis, and 3 as laryngeal tuberculosis. I also had the opportunity of examining the blood from the umbilical cord of a placenta delivered from a tuberculous mother.

In every case examined tubercle bacilli were observed. Sometimes only a few were seen, but they were mostly in large numbers, and clumps of 30 to 40 bacilli were not unusual, especially in the cases of acute miliary tuberculosis. In morphology most of the organisms were of normal size, though some short and even clubbed, as well as

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a few very long forms, were encountered. In one of these cases the pneumococcus was seen. In several cases clumps of tubercle bacilli could be clearly observed in some of the leukocytes, indicating phagocytosis.

In a patient in whom tubercle bacilli were found in the feces on two different occasions, and who upon physical examination did not present any signs of the disease, the organisms were found in the blood, and about 2 c.c. of the citrated sediment were inoculated intraperitoneally into a guinea-pig. This pig died in about three weeks from an internal hemorrhage (peritoneal). The lungs were studded with tubercles, four tubercles were present in the liver, enormous enlargement of the spleen as well as enlarged mesenteric glands were found at autopsy. Spreads made from the liver, spleen, kidney, heart's blood, and mesenteric gland contained tubercle bacilli, but no other organism.

In a second case diagnosticated as acute miliary tuberculosis 2.5 c.c. of the citrated sediment were inoculated intraperitoneally into a guinea-pig. This animal was sacrificed at the end of five weeks and presented the following lesions at autopsy:

Four bronchial glands ranging in size from 0.5 cm. to 1.5 cm. in diameter, several enlarged mesenteric glands, tuberculosis of the spleen, and only a few small tubercles in the lungs. Spreads from the spleen, mesenteric glands, and blood showed a few tubercle bacilli.

It appears that tuberculosis in all of its forms is a bacteriemia. Even in healing cases, or in those in which the disease is being arrested, tubercle bacilli are demonstrable in the blood, though usually in small numbers. In those dying of the disease, if histological examination of the liver, spleen, and kidney were made, one would find scattered throughout miliary, microscopic tubercles, which strengthens the above assertion.

Only a small number of cases are here reported, but it seems that even in this small number the constant finding, especially in cases of incipient tuberculosis, before the detection of the bacillus in the sputum, is quite a valuable procedure.

Again, it appears that the theory of mixed infection late in the

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disease does not always hold, for the reason that if tubercle bacilli are demonstrable by this method other organisms should be just as evident, and yet in only one of these cases studied was another organism—the pneumococcus—present. This patient had a pleural effusion, but was really in the incipient stage of pulmonary tuberculosis.

Discussion.

Dr. David Riesman: Dr. Rosenberger's communication appears to me to be of such great importance that it ought not to be allowed to go without discussion. If his results are corroborated, the discovery will mark an epoch in the history of tuberculosis. In two recent cases in my wards at the Philadelphia Hospital in which the diagnosis of tuberculosis was probable, but not definitely established, the bacilli were found in the blood by Dr. Rosenberger. One case was of particular interest; it was that of a boy who had been ill two weeks, and in bed only one week, with fever and cough. While the physical signs were suggestive of tuberculosis, the short duration, the continued fever, the general appearance, and the blood count made a suspicion of typhoid fever not unwarranted. The diagnosis of tuberculosis was, however, promptly confirmed by the discovery of tubercle bacilli in the blood, as well as in the feces and in the sputum. The other case was one of lead poisoning, in which on physical examination a very slight impairment of resonance at one apex was found. The ordinary symptoms of tuberculosis were entirely wanting, yet in the blood the bacilli were discovered, strengthening thus the evidence of the physical examination.

The method ought to be of value, not only in tuberculosis, but in other infectious diseases in which we may reasonably suppose microorganisms to be present in the blood. The Society has cause to be proud to have this subject first made public at one of its meetings.

Dr. F. R. Starkey: Dr. Rosenberger deserves the highest praise for the work he has done. Through his courtesy it was my privilege to see and follow the work through most of its course, and to note the great care taken by him with his technique and the absolute accuracy of his findings. It seems to me that

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these findings are going to upset some of our previous theories, especially the finding of tubercle bacilli in the placenta of the mother and in the blood of the infant, both of which I saw in the laboratory with Dr. Rosenberger. Our conception heretofore has been that of the transmission of a predisposition to tuberculosis, rather than of the actual disease; but there can be no question that the actual disease can be transmitted, when we find the germs in the placenta and in the blood of the mother and child.

I believe that this discovery is the most important that has been made in connection with the early diagnosis of tuberculosis since the discovery of the germ by Koch. It opens the question whether we all have tubercle bacilli circulating in the blood (since we are surely all exposed to them) which are only waiting for a condition to develop which will so lower our resistance as to permit them to attack us.

DR. A. J. SMITH: I should like to add my congratulations to those already expressed. I feel the importance of this paper, not merely as adding to the knowledge that we already possess regarding tuberculosis, but as pointing out some paths that may be profitably followed in our investigations concerning it. This discovery proves that there exists naturally in the system a certain amount of opposition to the activity of these organisms. If an individual with a small lesion in the lung has tubercle bacilli in the blood, yet does not have widespread miliary tubercles, there must exist in his system some means of antagonizing the infection. If the organisms often enter from the placenta of the mother into the tissues of the child, they must commonly be killed; because so few children of infected mothers show the disease afterward. We are thus born with a strong resistance to the bacilli, and it is quite possible that there may be discovered some way in which this tissue resistance may be increased in those parts of the body that are now the least resistant. The lymph glands and the lungs have from our present view the lowest grade of resistance to the tubercle bacilli. The striped muscles, particularly the voluntary, are rarely affected. It is extremely rare to find tubercles in the pancreas. One can pick out various parts of the body that scarcely ever show tuberculosis, although the tubercle bacilli are going through the blood and through all the tissues. There should be efforts made to discover what it is that immunizes the organism against the tubercle

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bacillus, what it is that we are born with that protects so many of us from the bacilli that have probably penetrated from tuberculous mothers into the blood of their children. I think that this paper has opened the door for a number of investigations that may lead to profitable conclusions.

DR. A. O. J. KELLY: I am only too glad to commend and encourage Dr. Rosenberger in his studies; perhaps the future will show that his paper is, as has been said this evening, epoch making, but I cannot forebear stating my conviction that his results should be accepted with the very greatest reserve. I am not prepared to believe that all tuberculous patients have circulating in their blood so many tubercle bacilli that they can be readily demonstrated by the simple, though excellent, technique that Dr. Rosenberger has devised. Especially do I not believe that tubercle bacilli can be readily found in the blood of a patient who has a tuberculous lesion in his lung so slight that an able clinician like Dr. Riesman is scarcely able to detect it. In this event why not many more cases of miliary tuberculosis, or why does miliary tuberculosis develop at all? I have no desire to disparage Dr. Rosenberger or his work, but I invite him to demonstrate the presence of tubercle bacilli in the blood by means of culture methods.

DR. D. J. MCCARTHY: This society treated the matter with a good deal of skepticism, when the question of the diagnosis of tuberculosis by means of bacilli in the urine was brought before it; and also, later, when Dr. Rosenberger exhibited the cases in which he had diagnosticated the disease by finding the bacilli in the feces. If these methods of diagnosis are held as valid, it is not difficult to see how in these cases, as in bone tuberculosis, the same conditions could exist. I may say that a study of infection of the meninges also points toward the position that there is a bacteriemia in the early cases. The fact that bacilli are found in the urine in cases without ulcerative lesions of the gastro-intestinal tract points to the view that there is, at least in a large number of early cases of tuberculosis, a tuberculous bacteriemia.

The idea advanced by Dr. Smith in regard to local resistance to tubercle bacilli is probably correct. I have done some experimental work by injecting tubercle bacilli into the carotid artery, without discovering any evidence of tuberculosis in the animals; yet the serous

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membranes are looked upon as points of easy infection for these organisms. In tuberculous meningitis there is always some condition causing lowered resistance present before the tubercle bacilli find lodgement. Some experiments done recently point to this conclusion.

December 10, 1908.

Two Instances of the Simultaneous Occurrence of Hypernephroma and Carcinoma.

By GEORGE B. FOSTER, Jr., M.D., and C. H. GERHARD, M.D.[1]

In 1896 Birch-Hirschfeld employed the term "hypernephroma" in describing certain neoplasms of the kidney, which up to that time had been variously classified as lipomata, sarcomata, carcinomata, endotheliomata, and adenomata.

The recognition of these growths as definite pathological entities was established by the contention of Grawitz, in 1883, that they arose from aberrant adrenal tissue, and for them he suggested the name *strumæ lipomatodes aberratæ renis*. Even now hypernephroma is rarely diagnosticated clinically, and that it may remain unrecognized even at operation is attested by the fact that so eminent a surgeon as Professor W. W. Keen thought one of these growths, which he removed before his clinic in 1900, a sarcoma, until enlightened as to its true nature by the pathological report.

It is not our intention to give an exhaustive review of the literature on hypernephroma in this paper, but it may be well to outline briefly the essential features of the condition, as established by the consensus of opinion of those who have studied the condition carefully.

Hypernephroma usually occurs in the fifth and sixth decades of life, is rather more common in men than in women, and like other malignant growths, appears to be influenced by heredity, a family history of malignant disease being obtainable in about 45 per cent. of the cases. Traumatism is apparently an exciting cause in some cases. The kidney is the site of election of these growths, but the

[1] By invitation.

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primary growth has been observed in many of the tissues of the body and, theoretically, may occur anywhere that primitive "rests" of adrenal tissue are found. The relative frequency of involvement of either kidney is a question which is open to argument; the statistics showing that in certain series of cases the right kidney was affected more commonly, while in other series, the left organ was attacked more frequently. Metastasis usually occurs by the renal veins, but may take place by way of the lymphatics, by contiguity, or by continuity. Metastases are most frequently found in the lung, but have been demonstrated in practically every organ of the body.

The histogenesis of hypernephroma is a much mooted question. It would seem, however, that the theory of its origin from primitive ectopic deposits of adrenal tissue, or "rests," is the most tangible one, inasmuch as it is most prone to occur along the genito-urinary tract, where these "rests" are found most frequently, and because of the resemblance of its histological elements to those of the adrenal glands.

The symptomatology of the condition is obscure, in some cases the growth giving rise to no symptom by which it could be recognized during life, as in our first case. The cardinal points upon which a tentative diagnosis can be made are the presence of a mass in the kidney region; pain, which may assume the character of renal colic, hematuria, and gastro-intestinal disturbances. The presence and recognition of adrenal cells in the urine may be the "straw which shows which way the wind blows." The blood picture is not constant. An *x*-ray examination may show the existence of the mass, but failed to do so in our first case. Cachexia appears late, if at all, and is not so profound as in other malignant growths. If recognized clinically there is but one course to pursue as regards treatment,—nephrectomy. Operation should be resorted to unless metastasis has occurred or the condition of the patient contra-indicates such procedure.

The following cases are of interest because of the association of hypernephroma with carcinoma of the stomach. The first case, which one of us (Foster) had the opportunity of studying daily in the wards of the Philadelphia General Hospital, presents the following points of interest: (1) The association of hypernephroma of the kidney with carcinoma of the stomach, the latter dominating the clinical

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picture; (2) the entire absence of symptoms, physical signs, or signs of research, which would even cause suspicion of its presence; (3) the tardiness with which cachexia asserted itself, especially as the condition was complicated by gastric carcinoma, the latter malady usually being characterized by a rather early onset of cachexia; and, (4) failure of the skiagraph to detect the growth, although, in justice to the skiagrapher, it may be stated that a small shadow was demonstrated in the kidney region upon reëxamination of the plate, after finding the growth at autopsy, which was thought to have been cast by the bony portion of the tumor.

Abstract of clinical history of this case:

CASE I.—Patient, a white adult male, aged sixty-eight years, driver by occupation, asked admission to the medical wards of the Philadelphia General Hospital on March 12, 1908, suffering with persistent vomiting and epigastric pain. Family history was negative. Patient chewed and smoked tobacco, drank three or four glasses of beer a day and an occasional whiskey, for a number of years. His past medical history was good. At the age of twelve he was confined to bed with "inflammation of the stomach." From that time on his health had been excellent. He denied venereal infection. His present illness began three months ago with belching of gas, sour eructations, occasional vomiting, gradually becoming more frequent, until now he can retain nothing but warm water. He had as much difficulty in retaining liquid food as in retaining solids. Epigastric distress also had grown progressively worse. He experienced gnawing pain in epigastrium, after abstaining from food for a few hours, which was relieved by eating. Anorexia was profound and bowels were habitually constipated. Weight had been reduced fifteen pounds since onset of illness. No history of hematemesis, jaundice, dyspnœa, cough, or œdema.

Points of interest in the physical examination were as follows: Body was much emaciated; color was good, and there was no evidence of cachexia. Conjunctivæ were muddy, otherwise the eyes were normal. Upper teeth missing, and only four careous "snags" remained in the lower jaw; gums and mucosa were atrophic. The pulse was regular, very slow (fifty per minute), of poor tension and volume. There was moderate radial sclerosis. Lymphatic glands

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were not enlarged. Examination of lungs revealed nothing abnormal. The heart outlines were normal. Muscle tone was poor in the mitral area. Aortic and pulmonic sounds were inaudible. The abdomen was scaphoid in contour; parietes flaccid; no tenderness or rigidity. Peristalsis could not be observed. Deep palpation in epigastric region caused patient some discomfort, but this did not amount to true tenderness. No palpable masses were detected. Normal area of liver dulness was slightly decreased. Spleen could just be palpated below costal margin. Percussion elicited tympany over entire epigastrium, apparently due to a dilated and ptosed stomach.

Laboratory Findings. Urine, amber, clear, acid, specific gravity 1.022, negative for albumin and sugar, showed the presence of an occasional hyaline cast, amorphous urates, and a few epithelial cells. Gastric contents showed absence of free hydrochloric acid, total acidity of 20, and the presence of lactic acid and Oppler-Boas bacilli. Feces, negative for occult blood. Blood examination showed 70 per cent. hemoglobin, 4,470,000 erythrocytes, and 7800 leukocytes. Differential leukocytic counts showed 62 per cent. polymorphonuclears, 28 per cent. small lymphocytes, 8 per cent. large lymphocytes, and 2 per cent. eosinophiles.

Second gastric analysis showed the absence of free hydrochloric acid and the presence of lactic acid and Oppler-Boas bacilli, with a total acidity of 20, confirming the first report.

Course of Disease. All food was withheld for the first twenty-four hours, the patient being allowed small quantities of hot water at frequent intervals. Concentrated and predigested liquid foods were then administered cautiously and vomiting was allayed. Four days after admission the patient's stomach tolerated a test meal, which was withdrawn with a stomach pump and submitted to the clinical laboratory for examination. A diagnosis of carcinoma of the stomach was made upon the report of the gastric analysis and a history of the case, although physical examination was negative. This diagnosis was confirmed by Dr. La Place, of the visiting surgical staff, who advised laparotomy. The patient refused to submit to the operation, began to grow stronger, and wished to get up. Condition oscillated between better and worse, with an occasional attack of vomiting and pain. No mass could be detected in the epigastrium, though watched

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for religiously. Three weeks after admission the patient began to fail rapidly, became cachectic, and on April 9 the right leg became swollen, edematous, painful, and the course of the saphenous vein was indicated by an indurated red line. In twenty-four hours it was almost black, and gangrene was feared. Two days later the patient died—twenty-seven days after admission and about four months from the onset of the disease.

The anatomical diagnosis at autopsy was: Brown atrophy of heart; chronic pericarditis; chronic mitral and aortic valvulitis; edema and congestion of lungs; metastatic growth (hypernephroma) of lung; atrophy of spleen; chronic interstitial nephritis, with hypernephroma; hypernephroma of renal vein and inferior vena cava, chronic hypertrophic gastritis with carcinoma; tuberculous ulceration of small intestine; secondary carcinoma of colon; cellulitis of right lower extremity.

Abstracts of the gross and histological descriptions follow: The left kidney weighed 110 grams; measured 11 x 6 x 6.5 cm.; the upper portion was enlarged; beneath the capsule over this enlarged part of the organ there were numerous elevated yellowish white areas varying in size; on cut section the upper portion was seen to be made up of a central tumor mass surrounded by stratified kidney substance, from which in places it was separated by bands of connective tissue. The cut surface of the new growth was yellowish white, semitranslucent and mottled with opaque, yellow areas of degeneration and with points of hemorrhage. The tumor was more or less lobulated. The renal vein was distended by a yellowish white mass, which was adherent to its walls. The inferior vena cava from the point of entrance of the left renal vein upward to the liver was occupied by a mass of tissue similar to that found in the kidney. This mass was adherent in places to the wall of the vessel. Histological examination of a section of a portion of kidney containing primary tumor showed the new growth taking up almost the entire section. Pressed to one side was seen a portion of the kidney, which was markedly sclerotic. In most places the tumor was separated from the kidney by a broad band of dense fibrous tissue, but here and there could be seen islets of the neoplasm lying in more intimate relation with the kidney substance. The tumor had a general lobular structure. The primary

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lobules were subdivided by strings of dilated capillaries, around which the tumor cells were arranged. There was no development of acini, but instead the lobule was made up of broad anastomosing columns of cells, between which were the capillaries. The cells lying on the latter and extending for some distance toward the centre of the column were cylindrical. Nearer the centre the cells were polyhedral in shape. The central portions were generally necrotic. The cells had abundant protoplasm taking the eosin stain, were at times vacuolated, contained from one to several nuclei rich in chromatin and with a metachromatic nucleolus.

A calcified piece of tissue taken from the central part of the tumor and examined by Dr. Karsner showed true bone formation.

Histological examination of a section of the renal vein showed the lumen occupied by a tumor mass similar to that found in the kidney. In most places the neoplasm merely pressed against the intima, but in several situations it was invading the venous wall reaching into the media.

Grossly, each lung contained a metastatic nodule, situated in the lower lobe lying under the pleura. On histological examination of one of these nodules it was seen to be made up of hypernephromatous tissue similar to that described under the kidney. Intracellular vacuoles were, however, much more numerous, the cell columns were narrower, and there was more of a tendency toward an alveolar arrangement of the cells. In one part of the section there was noted a vein which contained a tumor mass in every way similar, both as to stroma and tumor cells, to that surrounding it. At one place the vessel wall was infiltrated with the growth.

Grossly, the stomach was much contracted, measuring 10.5 cm. along the lesser curvature, the submucosa was thickened, and sent prolongations down into the muscular coat.

In the colon there were several areas in which the submucosa was thickened, the thickening being rather nodular in appearance and sending prolongations into the muscular coat.

On histological examination of a piece of tissue from the stomach the latter was seen to be the seat of a scirrhous carcinoma, which in several places could be seen taking its origin from the deeper portions of the mucous membrane, passing through the muscularis

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mucosa, and at some places extending into the muscular coat. Histological examination of one of the nodules found in the colon presented a similar picture, except that, although a number of sections were made, no connection between the glands of the mucosa and the cell nests and strings lying more deeply could be demonstrated, nor could any irregularity of the glands of the mucosa be detected, hence it might be inferred that the growth was a metastatic formation from primary gastric cancer.

The pancreas showed no change grossly. On histological examination the tissue was seen to be very poorly preserved. There was evidence of slight chronic inflammation.

In the records of the pathological department of the University of Pennsylvania we have encountered a similar combined occurrence of hypernephroma and cancer of the stomach.

CASE II.—This second case was that of a patient from Dr. Stengel's service in the University Hospital. The clinical history is brief—being that of a male, aged forty-nine years, whose illness dated back ten months previous to admission, starting with pain in the left hypochondrium coming on while lifting. Later there was loss of appetite with progressive loss of weight and strength. Physical signs were generally negative. Gastric analysis showed no free hydrochloric acid, the presence of lactic acid, Oppler-Boas bacilli, and blood stained tissue shreds. Blood examination was: Reds, 4,050,000; hemoglobin, 65; whites, 11,600. The autopsy was performed by Dr. Nesbit.

Abstracts of gross and histological notes follow: The right adrenal on section showed several nodules, measuring 2 mm. in diameter, pale, glistening, and firm. Histological examination of a portion of adrenal containing one of these nodes showed the tumor to be made up of a delicate connective tissue stroma containing many dilated bloodvessels and of parenchymatous cells arranged as branching hollow cylinders, in many instances lying directly on the capillary wall. The cells were rather large, rich in refractile protoplasm, polyhedral in form, with distinct cell wall. The nucleus was generally centrically placed, round or slightly oval in shape, rich in chromatin; the nucleolus stained metachromatically. The basal cells were often columnar in shape. Many of the cells contained large vacuoles with clearly defined margins. The neoplasm was not well marked off from the

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surrounding portions of the adrenal, merging almost imperceptibly with the latter. In some places immediately adjacent to definite neoplastic tissue there were islands of suprarenal parenchymatous tissue containing a cell or two exactly of the same size and staining properties as those of the tumor.

The stomach, grossly, presented the following appearances: It was normal in size and shape. Firm adhesions were present between the left lobe of the liver and the diaphragm. At the cardiac orifice, in the fundus, and generally in the cardiac half of the viscus the wall was diffusely infiltrated with an irregularly flat, ulcerative tumor mass. Stomach contents were bloody, foul, and decomposing.

Mesenteric and gastrohepatic glands were enlarged slightly and firmer than normal, but apparently not involved by the tumor.

The liver was uninvaded by the tumor.

Histological examination of a piece of tissue from the stomach showed only the muscular coat and peritoneum remaining. The upper portion of the former contained chains and nests of cells lying in the interfascicular spaces and extending to the surface. The superficial portions of the infiltrated muscle were necrotic. On contrasting the cells making up this neoplasm with those found in the suprarenal it was found that the former had larger, more evenly, and less deeply stained nuclei, the protoplasm was very much smaller in amount, and stained much more lightly. The cells were crowded together more, were not arranged as hollow branching cylinders, but in strings and nests, and occupied the spaces of the preëxisting tissue. There were no columnar cells present. Many karyokinetic figures were seen.

The pancreas, grossly, showed no change. On histological examination it was seen to be the seat of chronic interstitial inflammation, with fatty infiltration. In one area at the periphery there remained only the islands of Langerhans surrounded by fatty areolar tissue.

The writers have thought that the simultaneous occurrence of two such growths of malignant character is worthy of record, suggestive of a possible similarity of causation. Of course, there is possibility of coincidence of different causes. One might easily fancy, however, the presence of some chemical stimulus or the removal of some chemical restraint of growth operating at the same time upon the epithelium

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of the stomach and upon the cells of an adrenal "rest," or of the adrenal tissue itself. It is of interest to add that in the second case there were definite atrophic changes in the pancreas and that the well-known rapidity of growth and the vegetative appearances of the cells in many hypernephromata have some importance if one thinks of malignant tumors as arising, according to Beard's recent theory, from trophoblastic cells. However, even if one were to acknowledge the existence of some degree of value in Beard's suggestion, the sharp difference between the simultaneously occurring tumors would argue against the general applicability of his idea, since, if both types of tumors arise from unused germ cells, the tumors should have been identical, whereas in each case they are distinct and the metastatic growths have followed the type, now of one, now of the other. The occurrence of bone in the hypernephroma of the first case is in line with the suggestion which has previously been made that these adrenal tumors are in reality of teratomatous type, and adds somewhat to a restricted application of Beard's theory to this class of adrenal tumors.

In further comment upon the applicability of Beard's theory, it may be said that while it is true there existed definite atrophy in the pancreas of the second case, and a slight grade of chronic interstitial pancreatitis in the first, the grade of these changes was by no means excessive or beyond that which is found in a large proportion of autopsies on subjects without any neoplastic formations whatever.

In conclusion, the authors wish to acknowledge the courtesy of Dr. Frederick P. Henry in allowing the publication of this report, and also to thank Dr. A. J. Smith for his valuable suggestions and help in the preparation of this paper.

December 10, 1908.

Card Specimens Presented January 14, 1909.

DR. W. TAYLOR CUMMINS:

Mucoid Carcinoma from a Boy Fourteen Years of Age.

This specimen, a portion of the omentum, was removed at operation from a boy fourteen years of age. His illness began about six weeks before operation with watery diarrhea and vague abdominal

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pains soon followed by constipation, vomiting, and rapid emaciation; the abdomen became distended and tympanitic. A hard tender mass was felt just above the bladder and was thought to be either a malignant growth or tuberculosis of the mesenteric glands.

At the operation there was found a large mass protruding from the promontory of the sacrum, extensive adhesions between intestines and omentum, and thickening of the latter. The portion of omentum removed for examination shows some congestion; the surface is studded with small whitish areas resembling fat necrosis and three rather large fibrous nodules. On microscopical examination the nodules are found to be atypically glandular and made up of spheroidal epithehal cells in an advanced stage of mucoid degeneration supported by coarse fibrous trabeculæ. There is some infiltration with lymphocytes and eosinophiles.

DR. WILLIAM PEPPER:

Microscopical Specimens Showing Phagocytosis in Malaria.

Ten specimens were shown. The blood was obtained from a patient from Bombay suffering with double tertian and severe aestivo-autumnal malaria. In the blood were found a great number of macrophages which had evidently been ameboid; the fresh blood had not been examined. These macrophages are considerably larger than the normal leukocytes and are sometimes filled with perfect organisms though usually they contain only pigment or remnants of the organisms The peculiar shape assumed by them in this case led me to exhibit the specimens. One of the cells is drawn out until it appears like a worm, others have one or more pseudopodia extending in various directions. They are not artefacts. In aestivo-autumnal malaria macrophages are found, while in the tertian and quartian forms, the large mononuclears and polymorphonuclear neutrophiles act as phagocytes. While watching a tertian segmenter recently, I saw it rupture, and the spores spread throughout the field, having a slight movement of their own. Sometimes a group of two or three would be together. A leukocyte now came into the field, moved around, and began to eat up these spores. The method in which it went about this could not be called chemotactic. It

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moved like a living being going in different directions. It would pass one spore while in pursuit of another, and then double on its tracks and come back to get others, and in ten or fifteen minutes, it had devoured all of them.

DR. H. T. KARSNER for DR. ALLEN J. SMITH:

Microscopical Specimens from a Case of Leprosy.

The specimens of leprous skin were taken from a Chinaman who probably brought the disease with him when he surreptitiously entered this country on the Pacific coast. His death occurred in Harrisburg about one month ago as a result of advanced pulmonary and enteric tuberculosis from which condition he was suffering for several years.

A section of skin taken from a nodule on his ear showed the typical histology of a leprous nodule and contained many lepra bacilli when specially stained. A second section taken from the skin of the face a little anteriorly to the ear lobule showed the formation of a considerable amount of fibrous tissue suggesting an attempt at cicatrization at this point. Here also numerous lepra bacilli were demonstrated. Examination of the epithelium in this section showed a well marked dipping downward of the epithelial cells between the papilli of the corium, these extensions meeting a little deeper to form an interlacing network of epithelial bands and in some positions showing distinct formation of pearly bodies. Several sections cut in different directions were studied and the same appearance noted—evidently a beginning epithelioma.

Examination of the other viscera of this patient showed miliary tuberculosis and cloudy swelling of the liver, cloudy swelling of the kidney, congestion of the spleen, tuberculous enteritis and chronic ulcerative tuberculosis of the lungs.

DR. JAY F. SCHAMBERG:

Microscopic Sections of the Skin and Spleen from a Case of Indigenous Leprosy.

The patient from whom these sections were obtained was a woman who first manifested evidences of leprosy at the age of seventy and died six years later. She was born in this city and had never

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been beyond its precincts. The origin of the infection is unknown; her son was said to have been visited by two sailors supposed to have had elephantiasis. The patient was an inmate of the Municipal Hospital for some years where I had the opportunity of studying the disease and of ultimately making the autopsy. At the time of her death she exhibited distinct leprous nodules on the hands and face. Upon autopsy, no gross lesions of the viscera were observed. Sections were made from the skin, and from the liver, spleen, and other organs. Bacilli were found in abundance in the spleen and liver as well as in the cutaneous nodules.

Under the microscope there is exhibited a nodule from the skin showing the usual histological appearances. The section of the spleen which is also exhibited shows groups of lepra bacilli; some of these organisms are homegenous while others exhibit a dotted appearance. Some writers assert that the lepra bacilli, particularly in nodules undergoing involution, are dead. The inability to culture these organisms makes the truth of this assertion unverifiable. Unna has devised a special stain of carbol-fuchsin and methylene blue with which he claims to differentiate the dead from the living bacilli; the former are said to take the blue stain and the latter the red stain. Both Unna and Neisser have been able to stain bacilli black with osmic acid, and conclude therefrom that the bacilli contain fat. It is common to note considerable bacillary detritus in sections showing organisms. If the organisms are frequently dead, this would account for the numerous negative human inoculations.

The Histopathology of Experimental Urticaria Factitia, with Lantern Projection Demonstration.[1]

By T. J. GILCHRIST, M.D.,
JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND.

ABSTRACT.

Seventy-two lantern slides were shown, exhibiting the histopathology of urticaria factitia. Twenty-six cases of the disease had

[1] Read by invitation.

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been examined. The artificial wheal was produced by drawing the finger nail or the blunt end of a pencil rather sharply over the skin.

A portion of the wheal was excised, usually after ten to fifteen minutes had elapsed. In two cases of spontaneous wheals, sections were taken after five hours and twenty-four hours. In one special case portions of skin were excised after two minutes, five minutes, eight minutes, fifteen minutes, twenty-five minutes, forty minutes, and sixty minutes (all excisions being made with the full consent of the patient). Sections of the wheals from the severe cases showed marked edema of the connective tissue and its cells; profuse emigration of polynuclear leukocytes from the venules of the papillary and middle layer of the corium, and in some cases as deep as the subcutaneous tissues; pronounced fragmentation of polynuclear leukocytes and some fixed connective tissue cells; emigration of lymphocytes; the presence of fibrin and coagulated serum; apparent increase in the number of mast cells; swelling of the cells of the sweat-glands, so that the lumen was not easily distinguishable; dilatation of the lymphatic vessels, especially at the periphery of the wheal and deep in the corium; and a tendency of the fragmented detritus to be carried away by the lymphatics. In a few instances there were present evidences of apparent phagocytosis of mast cells, which had engulfed polynuclear leukocytes. The epidermis remained practically normal. Sections from older wheals (one hour) did not show so much fragmentation, but still very many polynuclear leukocytes were present. Sections from milder cases exhibited milder types of the same phenomena.

In one severe case, in which the wheal had been excised after two minutes had elapsed, there was present fragmentation of the nuclei of connective tissue cells. This seemed to demonstrate death of the cells preceding the inflammatory exudate.

In another severe case the polynuclear leukocytes were nearly all fragmented almost directly after leaving the bloodvessels. In nearly all the cases the wheals disappeared clinically in about one hour. The pathological picture is undoubtedly one of acute inflammation (Cohnheim); and the nuclear fragmentation is as remarkable as that produced by diphtheria toxin (observed by Dr. Welch after carefully going over the specimens). A feasible explanation of these phenomena is that a toxin is circulating in the blood, and when a wheal is

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produced this toxin is set free, producing necrosis followed by acute edematous inflammation of the whole corium, accompanied by marked nuclear fragmentation.

Discussion.

Dr. Louis A. Duhring: The similarity of the pictures from the different cases shows that the process is remarkably uniform, a fact that has for a long time been generally conceded. I think that the reader of the paper was one of the first, twelve or fifteen years ago, to bring out these points, especially that of the inflammatory character of the disease. Thirty or forty years ago, the inflammatory nature of the condition was not admitted by pathologists. It used to be thought that the disease scarcely came under the head of inflammation; but subsequent studies have proved conclusively that, as Dr. Gilchrist has stated, there is a distinct emigration of cellular matter from the blood.

An interesting point of view is the rapidity with which these products are thrown out and disappear. The causes that produce the condition are numerous and varied—even more so than has been expressed by the speaker; and some curious facts have been noted in connection with the production of urticaria. For instance, the injection of corrosive sublimate into the skin has sometimes been followed by no manifestation in the skin for twelve hours. This shows that some factor, probably connected with the nervous system, is at work, following the absorption of the corrosive sublimate. I believe that the central nervous system is concerned indirectly in most cases of urticaria. The fact that a wheal may be raised by pressure upon the skin indicates that the skin is in a peculiarly susceptible and irritable state.

I would make the remark that I believe that there are many conditions affecting the skin that are not true urticaria, but are urticarial. I have seen this in connection with several diseases. In erythema multiforma and dermatitis herpetiformis urticarial lesions may be a symptom. In these diseases the nervous system is the system at fault. I believe that we must go to the nervous system to account for most instances of toxic urticaria; but whether this will account for cases of

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factitious urticaria produced by nettles, jelly-fish, etc., I cannot say.

These conditions, to the casual observer, appear to be the same, but I should be inclined to separate them on the ground of general pathology. Serum-injections will sometimes produce urticaria; and so will various other agents and drugs, especially hypodermic injections of one kind or another—and sometimes long after the injection has been made.

DR. MILTON B. HARTZELL: I think that we must all agree that Dr. Gilchrist has demonstrated the inflammatory nature of the urticarial lesions that he has presented this evening. Certainly the changes that are to be seen are indicative of inflammation. There are two opposing views concerning the character of this disease. One, that it is angioneurotic, and the other, that it is inflammatory. Vidal, some years ago, demonstrated inflammatory changes in urticaria similar to those that we have seen tonight. Some years later, however, the wheals from urticaria were examined by Darier, who was unable to demonstrate any changes whatever. Unna regards the disease as an angioneurosis. It seems to me that it is quite possible that the wheal may be of different pathological varieties, that in certain forms of urticaria, particularly factitious, in which a small traumatism is inflicted upon the skin, the histological changes may be quite different from those in spontaneous lesions. This may be difficult to demonstrate; but it is quite possible, in considering the etiology, that we have to do with different processes in the different varieties of urticaria. It is well known that various causes may produce similar results. That it is a toxemia in most cases of the disease cannot be denied; but that it is not a toxemia in some cases cannot be denied either. A case has been reported in which the passage of a uterine sound produced it. It arises in so short a time after the ingestion of drugs that it is inconceivable that enough could have reached the circulation to produce this result. I have seen the entire body covered with wheals within five minutes after the ingestion of one or two grains of antipyrin. It would have to be a potent poison to produce such remarkable changes in so short a time. It is difficult to offer any explanation for the rapidity with which these changes occur. I think that the lesions demonstrated by Dr. Gilchrist are inflammatory in char-

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acter; but this does not prove that all urticarial wheals are of the same inflammatory character.

DR. JAY F. SCHAMBERG: I have been greatly interested in and enlightened by the lantern slide demonstration of the histopathology of urticaria factitia by Dr. Gilchrist. The photographs which he has projected upon the screen demonstrate that urticaria is an example of the most rapidly induced and evanescent inflammation known to pathology. The direct causation of the urticarial wheal, as has been intimated in the general discussion, has not yet been satisfactorily explained. It seems to me that, in the last analysis, all or practically all cases of urticaria may be assumed to be due to the circulation in the body fluids of some toxic or poisonous substance acting upon the blood-vessel walls. Whether the poison be injected by an insect, whether it be absorbed in the intestinal canal, whether it is injected beneath the skin in the form of an alien blood serum, the character of the lesion produced is much the same. Even cases of urticaria due to nervous shock may be explained by disturbance of innervation and the formation of autotoxins.

The projected photographs indicate very clearly that urticaria is an inflammatory disease. There is not merely a serous hemorrhage into the skin, as was once supposed, but also a great migration of cellular elements from the bloodvessels into the tissue. The edema is not only interstitial but also to an extent parenchymatous, the connective tissue cells participating in the process.

DR. GILCHRIST, closing: I thank you all for the appreciation and interest you have manifested in these demonstrations. It is of particular interest to the pathologist to see the demonstration of the occurrence of inflammation of the skin in such a short time.

In reference to Vidal: twenty-five years ago he showed the emigration of polynuclears in a wheal, but did not show the fragmentation of nuclei and of connective tissue cells, the phagocytosis, and the presence of fibrin. In the twenty-six cases that I have examined, these are shown. Ten years ago I was the first to demonstrate the migration of lymphocytes. One could explain the presence of mononuclears by the presence of lymphocytes only; in a number of cases one could see no mononuclears. In the milder cases, the same thing was seen in a milder form.

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In regard to the etiology and the production of urticaria by nettles, jelly-fish, etc., we know that the latter contain a substance that is inoculated into the skin, and that the urticaria is due to the inoculation of this deleterious substance. The same is true of nettle-rash. We have a definite substance producing an eruption, which is inflammatory. Strawberries will also cause an urticarial rash. Stimulation of the nervous system will not explain its production; it is an acute inflammation, with fragmentation, etc. In my opinion, it is caused by a toxin produced somewhere, probably in the intestines.

January 14, 1909.

Observations on Prophylactic Inoculations Against Typhoid Fever.

By HARLAN SHOEMAKER, M.D.

Sir Almroth E. Wright, of London, while on a visit to Professor R. Pfeiffer in 1896, was shown for the first time that typhoid bacilli killed by heat, when inoculated into a human being, produced, in the course of time, changes in the blood which were identical with those changes observed during and after convalescence from typhoid fever.

Wright, returning to England, took up this subject, which, as he expresses it, was destined, so far as he was concerned, to remain indefinitely inoperative, and published the results of two inoculations,[1] while Pfeiffer and Kolle published the results of their two inoculations.[2] However, E. Fraenkel,[3] reported the use of typhoid bacilli killed at 63° C. in the treatment of this disease as early as 1893.

Notwithstanding, to Wright belongs the credit of having developed and placed upon a scientific basis the prophylactic inoculation against typhoid fever. He prepared gratuitously 400,000 vaccines during the Boer War for the inoculation of the British soldiery, and made 4000

[1] Lancet, September 19, 1896.
[2] Deutsche med. Woch., November 12, 1896.
[3] Ibid., October 12, 1893.

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inoculations personally.[1] The appendix of this admirable report contains a bibliography of papers bearing upon immunity to bacterial disease up to the date of the publication by the author.

Criticism and opposition to Wright's method grew so strong that inoculation was discontinued in the British army. Subsequently the Army Medical School appointed a commisision to investigate Wright's methods scientifically and statistically. Colonel Leishman headed this commission, which was appointed October 21, 1904, and reported its findings in the *Journal of Hygiene*, 1905.

In this report a careful estimate is made of the effects produced in the blood stream by dosage, upon 1, a negative and positive phase; 2, stimulins *vs.* opsonins; 3, bactericidal substances; 4, bacteriolytic substances; and 5, agglutination. The entire report is confirmatory of Wright's experience, and still retains essentially his technique, with minor modifications.

CLINICAL OBSERVATIONS. On November 9, 1908, I inoculated four persons—two nurses, a doctor, and myself—with a typhoid vaccine, and the following symptoms were observed:

CASE I.—M. B., nurse. First dose of 0.33 c. c. In four hours local reaction at site of injection over insertion of deltoid muscle tendon to humerus, began with pain, swelling, heat, and redness. During second twenty-four hours temperature rose to 101° F. with malaise and general aches. Vomited. Was off duty two hours. During third twenty-four hours, sweats, normal temperature, and disappearing local reaction.

CASE II.—N., nurse. Dose and symptoms, both local and general, same as Case I.

CASE III.—Dr. M. Weight, 200 pounds. Dose, 0.66 c.c. Local reaction about site of inoculation very angry. Constitutional symptoms marked. Temperature 102° F. Vomited. Went to bed. Symptoms passed off in about the same order as in Cases I and II.

CASE IV.—Dr. H. S. Weight, 180 pounds. Dose, 0.66 c.c. Local reaction extended from shoulder to elbow, red and swollen, but not angry. Constitutional reaction, temperature 101° F. No prostration. Did usual amount of work. Had profuse sweat the

[1] See A Short Treatise on Antityphoid Inoculation, by A. E. Wright, M. D., published by Archibald Constable & Co., Ltd., London, 1904.

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two nights succeeding vaccination, with a disappearance of general symptoms.

GENERAL REMARKS. This experience is identical with that with which the Royal Army Medical Commission met when they prepared and inoculated themselves with a vaccine prior to their attempts upon volunteers. I thought that I had profited by their experience, but fell into an error from another source. As others may have a similar experience, I shall endeavor to point out one of the chief precautions necessary to the preparation and standardization of a vaccine.

PREPARATION OF VACCINE. The vaccine used for the first inoculation was prepared by washing off the twenty-four-hour growth from three agar slants and treating the same in a water bath at 53° C. for one hour; 53° C. is the temperature, and one hour the time, that the Royal Army Medical Commission found necessary to kill the bacillus typhosus. Here I found my chief difficulty because the strain of the Bacillus typhosus with which I worked, was not to be killed at this temperature. The saline solution (85 per cent. sodium chloride) of Bacillus typhosus germinated, and the vaccine was finally killed by prolonged heating to 55° C., when lysol, 0.25 per cent., was added as a preservative to the cooled vaccine. Lysol added to hot vaccine robs it of all activity.

Harrison,[1] gives the results of very eloborate experimentation in the preservation of vaccines of various sorts with a variety of preservatives, concluding that lysol, 0.25 per cent., is in every way a very safe margin for the prevention of contamination. He found 0.20 per cent. of this compound would sterilize tetanus, anthrax, and Bacillus subtilis in solution.

The degree of temperature at which various organisms yield the power of reproduction, evidently varies, not only with the organism under observation, but also with the strain of that organism. Not withstanding the fact that I presented to the society last year a paper[2] setting forth this important observation, I failed to apply it to Bacillus typhosus.

So every experimenter with bacterial vaccines, who wishes to arrive safely and expeditiously at a vaccine which retains the greatest

[1] Journal of Royal Army Medical Corps, 1907, viii, p. 472.
[2] New York Medical Journal, March 28, 1908.

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immunizing power, is cautioned, first carefully to ascertain the least degree of heat which is necessary to kill the strain. The strain of Bacillus typhosus used in my experiment had been obtained in August from the blood of a patient suffering with a profound typhoid intoxication. A twenty-four-hour broth culture of this strain was not virulent to a 250 gram guinea-pig.

Owing to the extreme motility of the organism, counting was difficult, and as the addition of formalin to the solution produced a slight amount of clumping, this method added nothing to the facility or accuracy of the count. The standardization of the virus was by Wright's method of enumeration, and was estimated to be 400,000,000 germs to 1 c.c.

It was the experience of the commission from the laboratory standpoint, as well as Wright's experience from his observations of those men to whom a second inoculation had been given, that they not only exhibited a greater agglutination, or Widal curve, but also, that there was no record of a single case of typhoid among them. A few cases of mild typhoid without mortality have been reported among those who had received but one vaccination.

SECOND INOCULATION. The proper interval for a second inoculation is ten full days. The Royal Army Medical Commission determined this interval by observation of the agglutination curve which begins to rise on the ninth day after inoculation, and attains its maximum height on the eleventh day. Here we see that the Widal reaction in the disease, as well as in the artificially produced agglutination is synchronous in its appearance. During the intervals of the inoculation, which should be ten full days, total abstinence from all alcoholic liquors must be observed. By still persisting in an unsuccessful effort to rob the germ of its reproductive power by an exposure to 53° C., the second inoculation was delayed several days. In my cases the second inoculation was given seventeen days later. The vaccine was killed at 59° C. for one hour—one degree lower than Wright originally recommended—and double the quantity was given, as previously stated. The constitutional symptoms were inconsider able, and the local reaction very slight. In my own arm where the needle penetrated the muscle, the inoculation produced pain immediately. This was not the experience with the first inoculation.

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PROTECTIVE SUBSTANCES IN THE BLOOD SERUM. Prior to the first inoculation the highest dilution of the blood serum with which it was possible to produce agglutination, varied from 1 in 7 to 1 in 10 in the four subjects. On the eleventh day after the first inoculation, the highest agglutination obtained was 1 in 12,872. This high tide mark fell somewhat. The second inoculation seven days later again produced a rising curve, 1 in 8,000 apparently being its limit. I also noticed a rise of the agglutination curve beginning about the tenth day after the second inoculation. This latter curve is not mentioned in the report of the British Commission.

No observations were made by me on stimulins *vs.* opsonins. The commission found the former over-balanced, the latter 2 to 1. Stimulin is that substance which is stable in the blood serum at 60° C.—that is, the blood serum which has been exposed to this degree of heat, loses its opsonin, and the substance remaining which prepares for phagocytosis, is called stimulin. Heated immune sera exhibited twice the power to stimulate phagocytosis as that observed in unheated sera.

BACTERICIDAL POWER. In my observations I found that the blood serum exhibited after inoculation, a bactericidal power in a dilution of 1 to 20. Viable bacteria when mixed with immune blood serum in the above dilution failed to produce colonies when spread over an agar plate and kept at 37.5° C. for twenty-four hours.

BACTERIOLYSIS. The immune blood serum of my cases diluted 1 in 4 to 1 in 6 and mixed with living Bacillus typhosus either produced spherulated forms, or a complete disappearance of the organisms. This was determined by spreading the serum mixture on cover slips and staining with methylin blue.

Prophylactic inoculation for typhoid is to be avoided in those cases suspected of an oncoming attack. Richardson,[1] in his experience of eight years in the treatment of this disease with bacterial products, reports a high mortality.

In this concise report I have endeavored to present the principal papers which have advanced this subject to its present status, and I have set forth briefly, my experiences with prophylactic inoculation

[1] Massachusetts Medical Society, 1907.

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which may aid in the solution of this intricate problem. One new point, that of the variation in the degree of temperature necessary to kill Bacillus typhosus, has been brought out. In the main I have endeavored to follow the most recent development in this subject as accurately as possible.

CONCLUSIONS. The evidence of bacteriolytic and bactericidal activity higher than the normal, and the presence of agglutinin, can be obtained from the serum of those who have been inoculated.

The immunity to typhoid conferred upon those officers and men of the 17th Lancers, inoculated, would seem to confirm the laboratory findings.

January 14, 1909.

Card Specimens Presented January 28, 1909.

DR. HERMAN B. ALLYN:

A Specimen of Carcinoma of the Stomach with Involvement of the Pancreas.

This specimen was obtained from a woman, aged fifty-four years, who was admitted to the Philadelphia General Hospital on October 3, 1908, and died January 5, 1909. She is known to have had the tumor since August, 1908. The carcinoma involved the pylorus and extended along the lesser curvature as an indurated, lobulated, ulcerated mass, mottled red and black, and covered with a dirty, viscid mucus. On the posterior wall of the stomach was a perforation 2 x 3 cm. in immediate contact with the omentum. On the anterior wall was another opening, 2 x 3 cm., closed by the under surface of the liver. There had been no perceptible leakage from either opening. The head of the pancreas was adherent to the pylorus, and seemed denser than normal.

DR. A. O. J. KELLY:

I. *Carcinoma of the Bladder.*

The specimen was obtained from J. M., a man, aged sixty-three years, who was admitted to the German Hospital July 11, 1908, and died January 5, 1909. His chief complaints were frequency and pain upon micturition of two years' duration, hematuria, pyuria, and

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emaciation. At the necropsy there was a very large cauliflower-like growth attached to the left wall of the bladder. It obstructed the left ureteral orifice, and had penetrated the wall of the bladder and invaded the perivesicular tissues. The left ureter was considerably distended and tortuous, and the kidney showed the common lesions of pyonephrosis. The right kidney was arteriosclerotic.

In connection with this another specimen was exhibited: A large cauliflower growth of the fundus and right half of the bladder, with consecutive bilateral dilatation of the ureters and pyonephrosis. The specimen was specially interesting on account of the enormous enlargement and thickening of the right ureter, which was about the size of the small intestine and its wall at least twice as thick.

II. *Gangrene of the Upper Lobe of a Lung in Association with Tuberculosis.*

The specimen was obtained from F. Z., a man, aged forty-one years, who was admitted to the German Hospital January 7, 1909, and died January 21, 1909. The patient stated that he had been well until ten days prior to admission, when he was taken ill with chills, pain in the right side, dyspnea, cough, and bloody expectoration. The necropsy revealed caseous pneumonia of the right middle lobe, chronic ulcerative tuberculosis of the apex of the right lower lobe and of the apex of the left upper lobe, and complete gangrene of the entire right upper lobe, which was represented by a mere shell composed of the two layers of the pleura adherent, lined with malodorous, shaggy, necrotic lung tissue, and containing a large amount of necrotic and gangrenous material. The disease, of course, was of much longer duration than the patient admitted.

III. *Hypernephroma of the Kidney.*

The specimen was obtained from W. W., a man, aged sixty-three years, who was admitted to the German Hospital January 22, and died January 23, 1909, of acute peritonitis. The hypernephroma was an accidental finding; it occupied the upper pole of the left kidney, and was about 4 cm. in diameter. It revealed the characteristic features of these growths, macroscopically and microscopically, since it was little if at all degenerated.

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DR. M. H. FUSSELL:

Primary Carcinoma of the Gall-Bladder.

This specimen was obtained from a woman, aged fifty years, who came to the Hospital a month before her death complaining of diarrhea and distress in the abdomen. She was found to have a right-sided pleural effusion and ascites. The latter rapidly increased, but the abdomen remained resonant throughout. The presence of fluid was diagnosticated by the fact that a wave could be obtained. The mass shown in the specimen is the omentum converted into a carcinomatous mass, made out during life, but thought to be the edge of the liver. The small intestine was covered with a recent miliary carcinosis. The gall-bladder was evidently the primary seat of the lesion and was filled with gallstones. There was a secondary growth in the liver.

Pseudodiphtheritic Septicemia, with Report of a Case Diagnosticated by Blood Culture.

BY GEORGE I. MACLEOD, M.D.,[1] AND FRED H. KLAER, M.D.

(From the William Pepper Laboratory of Clinical Medicine, University of Pennsylvania.)

THE exact relationship of the Bacillus diphtheriæ and the so-called "pseudodiphtheria" bacillus has been a subject of discussion ever since the discovery of the latter by Hoffman in 1887. The question as to whether the two organisms are to be looked on as members of the same group, the differences in their morphology and other properties being due to changes in their environment, or whether they represent two separate and distinct but probably allied groups, is still unsettled. The present tendency is toward the latter view. If this be accepted, the main practical difference between the two groups must rest on the ability of the true diphteria bacillus and the inability of the pseudodiphtheria bacillus to produce a specific toxin.

The more extended studies of recent years have demonstrated that while there is but a single species of the true diphtheria bacillus

[1] By invitation.

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which may, however, show slight variations in virulence, there are several species making up the group of "pseudodiphtheria" bacilli. Of these, some can be easily distinguished from the true bacillus by differences in morphology, staining and cultural characteristics as well as by their inability to produce toxin. Others again resemble the true Klebs-Loeffler organism so closely that the production of toxin is the only reliable distinguishing characteristic. The case we are about to report represents an infection with an organism of this latter group—an organism which can be very easily confused with the true bacillus.

The patient was under the care of Dr. MacLeod, and was seen on several occasions by Dr. Alfred Stengel.

A male, aged twenty-seven years, married, civil engineer, a temperate liver and of good habits.

His family history is unimportant and without bearing on the case.

He had had an attack of scarlet fever when seven years of age, followed in a few months by an attack of acute articular rheumatism of some severity. His heart was known to have been affected from this time, but it is uncertain whether the cardiac involvement followed directly upon the scarlet fever or developed in the course of the rheumatism.

From time to time he had suffered from rheumatic twinges, and had been treated frequently in the last few years for a pharyngitis diagnosticated as rheumatic. During the fall and winter of 1907 and 1908 he had three of these attacks, the last on February 16. In none of them was there any fever or other constitutional symptoms; the throat at each time remained quite free from lacunar or follicular exudate or membrane, presenting merely a severely congested appearance of pharynx and half arches.

On March 19 the patient arose feeling rather badly; his malaise, headache, and general condition of aching of the joints grew progressively worse, and at 7.30 that night he had a severe rigor. When seen at 8.30 P.M., his temperature was 104.2; pulse, 108; respirations, 24; his face was intensely flushed, the pupils dilated, and the lips rather cyanosed; his principal complaint was of pain of an influenzal character in the back and legs, together with the sensation of warmth to be expected from his rise of temperature. Examination of the

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throat, heart, lungs, and abdomen, was negative except for the cardiac murmur already referred to.

His condition gradually improved for the next few days.

On March 24 his temperature was normal, and he expressed himself as feeling better than at any time during his illness, even going so far as getting up to shave himself. Following the exertion, his temperature at 6 P.M. rose to 103.2°, his pulse to 122, and he was generally prostrated. The heart sounds for the first time were not to be easily separated, and a slight pericardial friction rub was present. The following morning, March 25, his temperature was 101°; pulse, 128; respiration, 38. Examination of the lungs was negative. Urinalysis showed a slight trace of albumin. The leukocytes were 17,800 and the Widal reaction was negative. The patient was in a weaker condition than at any time previous, his mentality apathetic, tongue heavily coated, and general condition typhoidal in character. His condition showed little change for the next week. On April 3 the blood examination showed 58 per cent. of hemoglobin, 4,530,000 erythrocytes, and 20,800 leukocytes. The differential count showed 79 per cent. polymorphonuclear leukocytes, 12 per cent. lymphocytes, 7 per cent. large mononuclears, and 2 per cent. transitionals in the 100 cells counted. The Widal reaction was again negative in dilutions of 1 to 50 and 1 to 100 in an hour. The urine was very highly colored, a brownish red, with specific gravity of 1020, acid reaction, a heavy cloud of albumin, no sugar, cylindroids and hyaline casts, a few epithelial cells and leukocytes. The test for bile was negative, while the test for urobilin was distinctly positive. Ehrlich's diazo-reaction was positive, and there was only a very faint trace of indican.

A blood culture was taken at this time in the usual manner from the vein at the bend of the elbow, about 15 c.c. of blood being withdrawn and distributed in bouillon and in agar plates, in all of which a fairly luxuriant growth occurred which in subcultures proved to be an organism similar to the Bacillus diphtheriæ. In view of the presence in the blood of what was thought to be the true Klebs-Loeffler organism, injections of diphtheritic antitoxin were given, but without the slightest change in the symptoms. On April 7 a second examination of the blood showed 34,320 leukocytes, of which

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there were 68.5 per cent. polymorphonuclears, 10.5 per cent. lymphocytes, 11 per cent. large mononuclears, and 11 per cent. transitionals in the 200 cells counted. A blood culture taken at the same time showed in five of the six flasks of bouillon, and in all six plates an organism similar to the one isolated in the first blood culture. A smear taken from the throat showed a mixed growth in which cocci seemed to predominate. A careful search failed to reveal any organisms resembling those found in the blood. From this time on to the day of his death, April 16, his condition became gradually but progressively worse. The heart sounds became one confused murmur, roughened in character, and transmitted almost all over the chest and back. The apex beat was diffuse and the heart somewhat dilated, more, however, to the left than to the right. A petechial eruption appeared especially on the legs and arms. Intense anemia and general wasting were present and the patient became semiconscious, finally passing into coma, in which condition he died after being sick twenty-eight days. There was no autopsy. The clinical diagnosis was pseudo-diphtheritic septicemia, with endocarditis following a chronic valvulitis.

In the case reported above, the great number of organisms in the blood was very striking. The agar plates, to which about 1 c.c. of blood had been added, each showed from 900 to 1200 colonies. This is considerably more than we have ever noticed in a long series of blood cultures in other diseases. On the agar plates the growth occurred as small whitish colonies, varying in size from a pin point to a pin head, moist, showing little tendency to adhere to the media. On Loeffler's blood serum the organism grew well as discrete pale yellow colonies. Smears from these showed a Gram-positive rod of irregular size and shape, with enlargements either at the end or at the middle, and the rods for the most part arranged parallel in small groups. The organism varied in length and width, the shorter forms being straight, the longer forms curved at one or both ends. With Loeffler's methylene blue the organisms showed rather marked differences in size and shape, and each organism took the stain irregularly. Neisser's stain brought out the polar granules to better advantage. The growth on agar was a thin uniform film fairly abundant, and smears here showed the organism to be larger, thicker,

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and more uniformly barred than when grown on serum; club-shaped forms were also common.

The growth in bouillon was quite characteristic. After twenty-four hours there was very slight general clouding; at the end of forty-eight hours, or, better, after seventy-two hours, a granular surface growth appeared with some sediment collecting along the sides and bottom of the flask, the fluid remaining fairly clear and of acid reaction. The surface growth on the slightest disturbance was precipitated through the liquid as a cloud and settled to the bottom. Milk showed a very slight acidity. No gas was produced in glucose, lactose, or saccharose agar, nor was there a visible growth on potato. As soon as suspicion had been aroused as to the organism being the Bacillus diptheriæ, about thirty surface colonies were picked up from the agar plates, emulsified in bouillon, and injected subcutaneously into a small-sized guinea-pig. The pig showed no signs of infection and was killed at the end of a week. Aside from a slight subcutaneous infiltration at the site of inoculation, no signs of disease were present. The same result followed the injection of even larger amounts of the culture from Loeffler's blood serum and bouillon when given subcutaneously or intraperitoneally. In one instance death did result in thirty-six hours, following an intraperitoneal injection of 4 c.c. of a forty-eight-hour bouillon culture in which had been emulsified the growth from a good-sized serum slant. At the autopsy there was an acute peritonitis with effusion from which the organism was cultured; cultures from the blood of the heart, however, were sterile. An effort was now made to increase the virulence of the organism by injecting very large doses of the culture subcutaneously into guinea-pigs, killing them the next day, culturing the organism from the site of inoculation, and injecting into a second pig. Several attempts to carry this out were unsuccessful, as we were not always able to recover the organism. In one set the organism was passed through three guinea-pigs without apparent increase in virulence. This, to be at all conclusive, should have been carried through a larger number of animals, but in the short series there seemed to be no change in virulence. The fact that bouillon cultures of this organism remained acid suggested a study of its fermentative ability as compared with that of a member of the pseudodiphtheria group.

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and of the true Bacillus diphtheriæ. Flasks of glucose bouillon, 1 per cent., were inoculated with each organism, and one flask was kept as a control, all being incubated at 37°. On successive days 10 c.c. were removed from each flask and titrated with $\frac{n}{10}$ sodium hydroxide solution, using phenolphthalein as an indicator. The amounts of the solutions used were too small for accurate results, but it was quite evident that the organism under discussion resembled more closely the true Bacillus diphtheriæ in the production of acid than it did the pseudobacillus. Loss of the culture by an accident prevented carrying out more accurate observations.

The organism found in this case then resembles the true Klebs-Loeffler bacillus so closely that practically it cannot be differentiated from it except on the basis of its not producing a specific toxin.

A search of the literature reveals few similar cases.

Roosen-Runge[1] reported a case of empyema developing after pneumonia in which nine days after resection of a rib, blood cultures showed an organism in pure culture similar to the diphtheria bacillus. Cultures from the pus of both pleural cavities before death and from the ulcerations on the tricuspid and aortic valves after death all showed an organism identical with that found in the blood. The growth in bouillon produced a marked acidity. Six guinea-pigs inoculated subcutaneously with the organism showed nothing more than slight signs of illness, while two inoculated intraperitoneally with 10 c.c. of a twenty-four-hour culture of the organism died in five or six weeks in cachexia and showed no signs of infection at death.

Mahler[2] reported a case of septicemia caused by the streptococcus and an organism similar to the diphtheria bacillus. After a mild angina the disease began with irregular fever, swelling of the cervical lymphatic glands, enlargement of the spleen and 19 days after the onset by a petechial eruption over the lateral aspects of the body in the axilla and on the elbows. Blood for blood cultures was taken on the 19th, 29th, 33d, and 40th days of the disease in the usual manner and placed in bouillon. The first culture after a week's growth showed an organism resembling the diphtheria bacillus. The last three cultures showed the same organism together with a streptococcus. It is interesting to note that no improvement followed the repeated injection of diphtheria antitoxin, while convalescence seemed

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to date from the injection of streptococcic antiserum. The bacillus isolated was not pathogenic for guinea-pigs when injected subcutaneously in doses of 0.5 c.c. and 1 c.c. of a twenty-four and thirty-six-hour bouillon culture, and caused only slight subcutaneous infiltration at the site of inoculation.

Ucke[3] reported a case of septicemia caused by the diphtheria bacillus following a mild angina and complicated by an abscess in the gluteal muscles, from both of which, as well as from blood cultures, organisms similar to the diphtheria bacillus were obtained. The blood was taken from the vein in the arm and added to several tubes of bouillon and slanted agar. From only one of these tubes (agar) did he obtain a growth of diphtheria bacilli. Before the gluteal abscess was opened, 3000 units of diphtheria antitoxin had been administered with no change in the condition of the patient. Recovery, however, occurred after opening and draining the abscess. One c.c. of a bouillon culture of the organism was injected subcutaneously into a guinea-pig of 260 grams weight. An infiltration developed at the site of injection, but did not kill the animal.

Von Niessen[4] found an organism similar to the diphtheria bacillus in the circulating blood in a case of combined scarlet fever and diphtheria. No mention is made of its pathogenicity.

Besides these four cases (if von Niessen's case be included) diagnosticated by blood culture during life, there are a number of instances where this same organism, so far as can be determined from the meagre description given, has been found postmortem.

Howard[5] reported an interesting case of ulcerative endocarditis in which at the autopsy, eight hours after death, an extensive thrombosis was found on the superior surface of the mitral valve and the evidences of septicemia in the other organs. Coverslip preparations from the mitral valve, the spleen, and kidneys showed in pure culture and in great numbers an organism which could not be differentiated from the Klebs-Loeffler bacillus except that it was non-pathogenic for guinea-pigs. The organism was studied by Welch, Abbott, and others, and by all was thought to be the true diphtheria bacillus.

Wright[6] reported a case of acute endocarditis in which the aortic and tricuspid valves were affected and in which cultures postmortem showed the pneumococcus, staphylococcus, and an organism corre-

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sponding to the Klebs-Loeffler bacillus except that it was non-pathogenic for guinea-pigs.

In the cases so far reported the infection has not had any direct connection or relation with the disease ordinarily known as diphtheria, and in every instance except possibly in von Niessen's case the organism was non-pathogenic for guinea-pigs.

We have been unable to find the record of any case of true diphtheria in which diphtheria bacilli pathogenic for guinea-pigs have been found in the blood during life. Many instances, however, are recorded where the organism either alone or with the streptococcus or staphylococcus has been found in the blood and internal organs after death. Such cases are reported by von Babes,[7] Kolisko and Paltauf,[8] Johnson,[9] Nowak,[10] Frosch,[11] Kutscher,[12] Booker,[13] Flexner,[14] Cannon,[15] Wright,[6] Wright and Stokes,[16] Stokes,[17] Kanthack and Stephens,[18] and Pearce.[19] In many of these cases the distribution of the bacilli was so general that it must have occurred before death, so that we feel that the bacilli could have been isolated from the blood in these cases had they been cultured during life. Unfortunately many of these reporters do not state whether the organisms found by them were pathogenic for guinea-pigs. Wright, however, in his work found that all the organisms isolated by him from fatal cases of true diphtheria were pathogenic for guinea-pigs, except one to which reference has already been made.

Pearce[19] says "the clinical significance of this general infection with the Klebs-Loeffler bacillus is not apparent. It occurs generally, but not always, in the gravest cases, or those known as 'septic' cases. It is probable that it may be due to a diminished resistance of the tissue cells, or of the germicidal power of the blood. Whether the Klebs-Loeffler does or does not continue to produce its toxic products, wherever it may be, in the blood or internal organs it is impossible to say, but from the number of fatal cases with such an infection, it would seem very probable that it does."

In the cases reported we seem to have two groups of organisms which resemble each other more or less closely in morphology, staining properties, and cultural characteristics, but differ from each other in the ability to form toxin when injected into guinea-pigs The one group seems to have been definitely identified as the true

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Klebs-Loeffler bacillus and the question arises as to whether the other group is to be looked on as an entirely distinct but allied group or whether it is a true diphtheria bacillus which has under peculiar conditions lost its power of producing toxin.

A study of the conditions under which this interchange of pathogenicity could take place has been made by a number of observers. Of the results of this work, Graham-Smith, in his exhaustive treatise on diphtheria published in 1908, states that "experimental attempts to artificially decrease the virulence of diphtheria bacilli produce somewhat conflicting evidence, but show that under any conditions their attenuation is a matter of difficulty and uncertainty. Attempts to give virulence to totally non-pathogenic diphtheria bacilli have been almost uniformly unsuccessful and even attempts to raise the virulence of lowly virulent bacilli have frequently failed."

Again, "it has been asserted that Hoffman's bacillus (the form usually referred to as the pseudodiphtheria bacillus) may be pathogenic to man but no bacteriological proof has been produced, and except by one or two observers Hoffman's bacilli derived from all sources have been found to be non-virulent to guinea-pigs in fairly large doses."

The opinion seems to be gradually gaining ground that the diphtheria bacillus and the pseudobacillus represent two allied but separate groups of organisms. Hamilton[20] in a thorough critical review of the literature shows that the various methods proposed in the past for differentiating these two groups have not been satisfactory and decisive. She quotes the opinion of Beck, Loeffler and Spronck that "it is impossible to distinguish the true from the pseudobacillus by means of cultural pecularities, morphology, presence of Neisser granules, chemical activity or virulence for animals, and the only hope for a sure method of differentiation lies in the application of specific sera to neutralize specific toxins."

After a careful study of 29 organisms which were, with the exception perhaps of three, pseudodiphtheria bacilli, she concludes that this indefinite group "may be divided into at least three separate groups. First, there is the group of those which are non-pathogenic to guinea-pigs—a group which probably should be further subdivided, for some are apparently pathogenic to man and there are

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certainly decided differences as far as cultural characteristics go, yet a basis of subclassification would be hard to find. Second, there is the well-defined group of organisms pathogenic to guinea-pigs, producing a general bacteriemia, and neutralized by the serum of a rabbit immunized against one member of the group; third, the organisms which form gas in glucose media, produce bacteriemia in guinea-pigs, and are neutralized neither by diphtheria antitoxin nor by the pseudodiphtheria serum."

Graham-Smith comes to much the same conclusion when he says that "evidence is rapidly accumulating to show that many other species of diphtheria-like organisms besides Hoffman's bacillus are to be found in the throat, nose, eye, genital tract, and on the skin of healthy and diseased persons, some of which more closely resemble the diphtheria bacillus and others Hoffman's bacillus in character."

H. M. Goodman,[21] after a careful study of the three types of the diphtheria group, the Bacillus diphtheria, the Bacillus pseudo-diphthericus, and the Bacillus xerosis, concludes that "separation of the members of the diphtheria group into two or more species on the basis of morphology, staining properties, character of growth or pathogenicity is not justifiable because of inconstancy. The same applies to immunity reactions which have the additional objection that their significance as species reactions is as yet unknown. The only character which experience has not shown to be untrustworthy is that of difference in behavior toward carbohydrates," and this he does not consider a species characteristic because "it can be readily and markedly altered at will by artificial selection." We feel that his conclusions are sound in regard to the interchangeability of different characteristics with the exception of pathogenicity. He proved quite conclusively that by natural selection an *increase* in toxicity for guinea-pigs could be brought about in the diphtheria bacillus, but we are not convinced that he has shown that this can be depressed entirely nor that it can be added to those forms which usually do not possess virulence.

Zinsser[22] has recently confirmed the opinion of Knapp that these groups may be differentiated by their fermentative action on certain sugars, the true diphtheria bacillus fermenting dextrin but not saccharose, the xerosis bacillus fermenting saccharose but not dextrin,

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and the pseudodiphtheria bacillus not fermenting either. We did not apply this test to our organism. This may prove to be a satisfactory method of differentiation, but as yet the difficulties of carrying it out prevent its use as a practical method.

From these opinions and quotations it seems reasonable to look on pathogenicity for guinea-pigs as the only reliable difference between the true and the pseudodiphtheria bacilli. In the cases reported above (except those diagnosticated as true diphtheria) the organisms have been considered diphtheria bacilli, in some cases being specifically called Klebs-Loeffler bacilli. With our present knowledge we fail to see the grounds for this opinion.

We feel, therefore, that we are justified in looking on the organism found in our case, and also probably those found antemortem in the cases reported by Roosen-Runge, Mahler and Ucke, as well as those reported as found post-motem by Howard and Wright, as belonging to the group of pseudodiphtheria bacilli, and for them would suggest the term diphtherioid bacilli to differentiate them from Hoffman's bacillus on the one hand, from which they can be distinguished by morphological and cultural characteristics, and especially by the production of acid in bouillon cultures and from the diphtheria bacilli on the other, from which they can be distinguished only by their inability to produce toxin when injected into guinea-pigs.

Further work is necessary on the pseudodiphtheria group before a proper classification can be arrived at. This may also bring to light a method for differentiating the members of this group from the true Klebs-Loeffler bacillus, which will be shorter than the one we have now which depends on guinea-pig inoculation. We would repeat the suggestion made by others that pathogenicity for guinea-pigs, which can be neutralized by diphtheria antitoxin, is the only crucial test for the true Klebs-Loeffler bacillus.

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Recent Advances in the Physiology of Saliva, Together with Certain Aspects of its Pathology.

By EDWARD H. GOODMAN, M.D.

No article on any branch of the physiology of digestion can be written without due acknowledgment of the inspiration derived from the colossal researches of Pawlow. From the Institute of Experimental Medicine in St. Petersburg, at whose head he stands, have emanated papers which have revolutionized, from a physiologist's viewpoint, the whole aspect of the digestive tract, but which have been wofully neglected by the medical world in general. To present in compact form some of these researches and those of other physiologists is my object at this time.

As soon as food enters the mouth there is a more or less abundant secretion of saliva. This is derived for the most part from the three pairs of salivary glands—the parotid, the submaxillary, and the sublingual—and also from the numerous small glands distributed over the tongue, inner surface of the cheeks and lips, hard and soft palate, and pharynx.

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The chemical composition of the saliva from all the glands, the mixed saliva, varies with many factors, the principal one being the relative activity of the different glands, this being in turn determined by the character of the food ingested. The normal saliva has about the following composition:

	Jacubowitsch.	Hammerbacher.
Water	995.16	994.20
Epithelium	1.62	2.20
Soluble organic matter	1.34	1.40
Potassium sulphocyanide	0.06	0.04
Inorganic salts	1.82	2.20
	1000.00	1000.04

The main ingredient of the saliva is water, which amounts to 99.5 per cent. of total saliva. The soluble organic matter is protein in nature, and consists of a mixture of mucin, globulin, and serum albumin. Potassium sulphocyanide is supposed to be derived from the parotid gland (Brubaker),[1] but researches of de Souza[2] have shown that this is extremely improbable, the evidence being very strong that it is a waste product of metabolism in the blood, which is excreted by the salivary glands in proportion to the other salts. These salts consist of sodium, calcium, and magnesium phosphate, sodium carbonate, and sodium and potassium chloride. This is supposed to be a normal constituent of the saliva.

The normal saliva is frothy and opalescent, slightly turbid, and somewhat viscid. The specific gravity is generally estimated as between 1003 and 1006. It is usually alkaline in reaction, though it may be neutral, and, indeed, even acid. The latter depends usually on fermentation of food particles in the mouth, and is seen in certain disorders of the alimentary tract. The amount excreted per diem is variable, but Dalton[3] estimates the quantity at about 1305 grams.

The saliva excreted by each of the three main salivary glands has not the same composition, that of the parotid being clear, limpid, non-viscid, alkaline, specific gravity, 1003; that of the submaxillary gland being clear, slightly viscid, alkaline, specific gravity, 1002, while the saliva from the sublingual gland is clear, very viscid, and strongly alkaline. An essential difference between the parotid and submaxillary salivas is the absence of mucin in the former and its

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abundance in the latter. The importance of these various compositions will be seen later when we speak of the adaptation of the salivary glands to specific excitants, that great discovery linked forever with Pawlow's name.

PHYSIOLOGY OF SALIVARY SECRETION. The work done on this subject by the Russian school under Pawlow's direction, and by physiologists of other countries under his influence, has become so voluminous that to trace step by step the development of our present knowledge would not only be too long a task, but would serve no object but that of historical interest. If the need for a universal language has ever existed, this fact must have been apparent to anyone who has tried to acquaint himself with recent advances in the physiology of digestion. Most of the best work is inaccessible to the majority of medical men, owing to the fact that many of the important papers have been published in Russian journals. There are in every readable article references to some Russian work, and full references, too, but this does not satisfy one's desire for reading the original report and drawing one's own conclusions from the perusal. It was, therefore, with much, but not with entire, satisfaction that the appearance of a German translation of Prof. Pawlow's lectures was hailed. In this small book (printed in English four years later) Pawlow[4] presents in an engaging manner the results of work carried on in his laboratory.

It is a well-known fact, and has been for many years, that when the stomach is empty and there is more or less hunger, the sight of food is sufficient to start a salivary flow, and this important fact has become incorporated in the familiar expression, "It makes my mouth water." This psychic prelude is what Pawlow terms "intense desire for food," and he regards this as an undoubted stimulus to the centre of the nerves going to the salivary glands. Another instance of a fact long observed in everyday life, and as long misinterpreted, is the flow of saliva when food is taken into the mouth. Heretofore it has been generally thought that practically everything entering the buccal cavity excites reflexly the salivary glands, the intensity varying with the strength of the stimulus. This impression was responsible for the long undetected specific excitability of the peripheral endings of the centripetal nerves of the digestive tract, which

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is generally regarded as one of the most important biologic advances. It is true that a great many substances act as stimuli to the salivary glands, and the complex physiologic nature of the saliva has probably interfered with a clearer understanding of the specificity of the stimuli.

Saliva, under normal conditions, is the first digestive fluid encountered by food, and its functions are numerous and important; it moistens dry substances, acts as a solvent on soluble foods, covers hard bodies with mucus so that their transit through the esophagus to the stomach may be facilitated, and it helps in the digestion of starchy foods. Saliva acts as a sort of refinery, for many things entering the mouth are useless and even harmful, and it is the purpose of the secretion to separate the good from the bad, and to render dangerous substances innocuous, or else to remove them entirely from the digestive tract. If the substance is an acid, its destructive action is, to a certain extent, modified by the alkalinity of the saliva; if the substance be a caustic, its concentration is lessened by dilution with saliva. If, on the other hand, the substance must be entirely removed, the saliva acts as an irrigator, washing it away and preventing its absorption by the blood. Pawlow says this last function has been practically neglected by physiologists, and yet we know how often we have an increased flow of saliva on feeling disgust for anything, or when we have distaste for a certain food. Moreover, for a long time, it suffices one only to think of the bad taste or the unpleasant appearance of a food or object in order to excite again the salivary flow. This salivation is just as intense as we notice when the sight of food pleases us, and yet the object is entirely different, in the first instance being to wash away the offender, in the second, to make its reception by the remainder of the intestinal tract more easy.

Based on these observations, Pawlow asserts that the reason substances introduced into the mouth cause a secretion of saliva is because they have a definite physiologic action, and not because the glands are excited by any kind of stimuli. This view has been well substantiated by the experiments of Dr. Glinski on dogs with salivary fistulas. In the one dog with a submaxillary fistula a flow of saliva followed mere showing of meat, eating of meat, introduction of sand

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into the mouth, and painting of the mucous membrane with acid; in fact, it would seem that there was no selective action of the gland to stimuli. On the other hand, a dog with a parotid fistula secretes no saliva on being shown meat, and, what is more remarkable, does not respond even when given meat to eat. But if finely powdered *dry* meat is given the animal there is an abundant secretion. Moist bread has no exciting effect, but if dried, there is a great increase of saliva. Wulfson added to the experiments of Glinski by observing that dogs excreted more parotid saliva on being shown dried meat or bread than they did with fresh; and it would appear from this that there is a definite and selective action of the salivary glands to stimuli, and the stimulus in this instance is the dryness of the food.

The new field of research opened by Pawlow's operative technique and keen observation of phenomena has been frequently tilled by recent observers. Malloizel[5] made some careful studies on the secretion of the submaxillary gland, and from his work have been gleaned important facts. In the first place, he found there was a definite time between the application of the stimulus and the appearance of saliva. Heat excited the salivary flow the quickest in from two to three seconds; but almost as quick a reaction was noticed after ingestion of distasteful substances, as sodium chloride and quinine sulphate. The quantity of saliva was greatest with the last two substances, greater than with meat. The viscosity increased if the substance ingested were to be digested; for instance, a very watery, slightly viscid fluid followed the putting of salt, quinine, or sand in the mouth, while meat aroused a very viscous, thick, mucin-rich saliva.

The pyschic factor was very strong in dogs, and stimuli were found to be discharged by the auditory, olfactory, and visual fibers. If the experimenter reaches in his pocket for a lump of sugar, clicking pieces together at the same time, and then gives it to the animal to eat, it suffices thereafter merely to put the hand into an empty pocket, or to click lumps of sugar together, or to show a piece of sugar, in order to induce salivation.

As regards the ferment content, Malloizel has pointed out that the diastatic activity of the saliva varies a great deal, and that the submaxillary saliva is always less active than the parotid. Meat

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and foodstuffs in general produce a ferment-rich saliva, while quinine sulphate and salt and such substances are followed by a secretion poor in ferment.

The conclusions to be drawn from the above facts are, in the first place, a corroboration of the teaching of Pawlow, that saliva neutralizes and dilutes deleterious substances by an increased flow, which, being less viscid, and hence poorer in mucin, serves to wash away the offending body. On the other hand, when a substance is to be swallowed, a viscid, mucin-rich saliva is poured out to make its passage through the esophagus easier. Malloizel has also confirmed Pawlow's epoch-making discovery of the adaptation of the salivary glands to specific stimuli, and has shown that these stimuli act always the same: a substance which has caused salivation is followed by the same phenomena whether the substance be a solid, in solution, or a vapor, and whether it be ingested, seen, smelt, heard, or even if the animal only imagines he is going to get it. A more brilliant and more conclusive instance of the "Anpassung der Verdauungsdrüsen" can scarcely be imagined.

Von Zebrowski[6] enjoyed the opportunity of studying a patient suffering with a parotid fistula, and his conclusions to a certain extent agreed with those of Malloizel. The secretion he found to vary with the composition of the food, and the rapidity of the secretion was influenced by the quantity of the stimulus (foodstuff). The intensity of the latter increased the rapidity of the secretion, and to a certain degree the composition of the saliva. Mastication was found to exercise a marked influence on the flow, as it causes rubbing of foodstuffs against the mucous membrane with a prolongation of their stimulative action, whereas the action of a stimulus in the absence of chewing is but superficial and transient. Substances requiring much chewing produce thick saliva, while mastication, in its turn, depends on physical structure of the excitant. Unilateral chewing is accompanied by more secretion from the gland situated on the side the seat of masticatory action, while the opposite gland is less active, and secretes a saliva containing more organic substance. On the latter, to a certain extent, depends the digestive power of saliva. The mixed saliva is necessarily an aggregate of the secretion of the various glands, and its composition varies with the stimuli affecting

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them. The proportion between the amount of food taken and the amount of saliva secreted is wonderfully regulated.

Let me recapitulate briefly: Salivary flow is excited not only by foodstuffs, but by foreign bodies as well. All dry powdery substances and all substances with pronounced acid or alkaline properties, many salts and organic bodies, call forth a large amount of saliva. Strangely enough, water has no effect, and if the dry foods are mixed with water there is a marked decrease in the quantity of saliva secreted. Foreign bodies, such as gravel, cause no sialorrhea, for the dog removes the stones with the tongue; but if sand be thrown into the mouth, there is a profuse secretion, as the animal must adopt this defence, the particles being too minute to allow of removal by the tongue. The saliva in this case is very watery and contains little mucin, for its action is to be a purely mechanical one; whereas the saliva poured out on food is thick, viscid, and mucin-rich, to aid its passage through the esophagus. The parotid gland has a distinctive antidotal function in the case of acids or caustics, for against these is formed a cloudy, albuminous saliva, the object of which is to form a chemical combination with the substance.

Neilson and Terry[7] have shown that in the dog there is an adaptation of the saliva secretion to diet; also that the amylolytic power increases with the ingestion of starchy food, and others have arrived at the same conclusion.

The psychic factor in exciting the flow of saliva is so well known since Pawlow's researches that it will suffice to close the discussion of this part of the subject with an illustration given by Malloizel.[8] A dog, in which a submaxillary fistula had been made, was put in pursuit of game, and on bringing it back there was a viscid fluid exuding from the fistulous opening. One day a magpie was killed and the dog was sent to retrieve it. The incentive of pursuit and the excitement of the sport had caused a mucous secretion to appear from the submaxillary gland, but as soon as the animal saw the bird, which, to most dogs is a distasteful object, the viscid secretion stopped and was replaced by a liquid fluid.

NERVOUS MECHANISM OF SALIVARY SECRETION. Under this heading will be discussed not so much the nervous mechism, as it is generally understood, as the nature of stimuli. The views concern-

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ing the purely anatomical paths that nerve impulses take have not changed any under the sharp survey of modern science, whereas our knowledge of the salivary reflexes has been considerably modified. We have seen that the first stimulus of salivary secretion is the psychic moment; as witness the effect caused by the sight, smell, or even thinking of food. Such a reflex has been called by Pawlow, conditioned, to distinguish it from the unconditioned reflex or that aroused by food entering the mouth.

The experiments of Tolotschnioff[9] have shown that the conditioned reflexes become weaker on repetition until they finally disappear, although they may be easily re-aroused. This is brought about by allowing the animal to taste the food, or the reflex may be reactivated by putting acid in the mouth. On the other hand, if the conditioned reflex has been first aroused by an acid, and has disappeared on repeated tempting, one may re-arouse it by putting meat or acid in the mouth; it even reappears if meat is put in acid and held before the animal. This is very remarkable, as it will be remembered meat *per se* usually calls forth a small amount of saliva.

As might be supposed, conditioned reflexes appear only when the animal is hungry, and the individual properties of a stuff, as for instance, smell, act at a distance, much weaker than the stuff itself (eating). If a profuse flow of saliva has been excited by dry bread, the same disappears if the dog is shown a piece of raw meat; also, the salivary flow aroused by dry bread is decreased if another dog is given bread to eat.

Water, as is known, is not a stimulus to the salivary flow, but if one gives a dog a black-colored, acid fluid to drink, the mere showing of black-colored water excites the saliva. The apparent relation between the black color and the saliva may be stopped if one begin the experiment with black water instead of acid, showing that the black color is not the stimulant. If a substance is shown a dog the properties of which he is entirely unfamiliar with, no salivary flow is seen. If, however, he be allowed to taste it, and if he find it agreeable, the mere showing thereafter excites a secretion.

As an illustration of how apparently immaterial moments associated with feeding or tempting the animal can increase or excite the salivary secretion, Babkine[10] states that if the dog's saliva has stopped as a

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result of persistently waving a piece of meat before his eyes, it can be re-aroused merely by waving the hand of another person. The same author also showed that motor or sensory disturbances held the relative reflexes in abeyance, as vibrating the animal's body, ringing a bell, sudden lighting of the previously darkened room, or new sounds, as a trumpet or graphophone.

Pawlow explains the origin of the condition reflex by supposing the arc of an unconditioned reflex to be formed of the centripetal nerve endings of the buccal cavity, centripetal sensory fibers, subcortical sensory centre, subcortical salivary centre, and the secretory fibers of the salivary glands. If, now, other centripetal fibers, such as are connected with vision and olfaction, are repeatedly and simultaneously aroused, together with their subcortical and cortical centres, there are, he thinks, connections formed from these to the cortical, and from them to the subcortical centres, and these are, after repetition, able to transfer an impulse from the extrabuccal centripetal nerve endings over the cortical centres to the secretory fibers.

Pawlow believes that the constant disappearance of the conditioned reflex after repeated stimulation and its sudden recurrence under certain conditions are due to fatigue of the cortical centres. He offers two facts which apparently prove his theory: (1) The conditioned reflex disappears spontaneously and reappears just as spontaneously after a couple of hours. (2) The conditioned reflex disappears more rapidly if the stimuli are more rapidly repeated. The re-appearance of the conditioned reflex after introduction of an unconditioned or another conditioned reflex is explained by supposing there is a reflex arc formed by the new stimulus from the subcortical, not the tired cortical centre.

That the salivation aroused by tempting an animal with food should stop when another dog receives it to eat, Pawlow supposes to be due to inhibition sent out by the salivary centre to the severely aroused dynamic centre, which may be an "Unlustzentrum."

The above facts have been gathered from a fascinating paper by Meisl[9] on the application of Pawlow's teachings to psychology, and it would well repay those interested to read the original article.

Regarding the adaptation of salivary glands to specific stimuli we have spoken enough, but a word may be said with profit concern-

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ing the property the buccal cavity possesses of limiting certain stimuli to certain locations. We have learned that the salivary glands are specific for certain substances and the question naturally arises, how does the organism know which saliva to pour out? Systematic experimentation has shown that many substances act strongest when put on the root of the tongue and are entirely without effect if brought in contact with the soft palate. The converse also holds good. Heimann (quoted by Boldyreff[11]) has concluded that chemical, thermic, painful, and mechanical stimuli all cause salivary flow, the action varying with the place of application.

Chemical stimuli were found to act strongest on the mucous membrane of the tongue, and more intensely at the base, less strong at the tip and weakest on the inferior surface. Of all the chemical stimuli, bitter and sweet stuffs are especially characteristic.

Thermic stimuli produced the strongest flow of saliva if applied to the dorsum of the tongue, under the lips and the lateral aspects of the upper lip. Next in intensity are the middle part of the upper lip, hard and soft palate, and tip of tongue, while the weakest salivation results from applying stimuli to the mucous membrane of the cheek.

The entire buccal cavity is acted upon by painful stimuli with the exception of the cheek, while mechanical stimuli act strongest on the dorsum of the tongue and soft palate, and less strong when applied to the hard palate, upper lip, and tip of the tongue.

SALIVARY DIGESTION. The main digestive function of the saliva, apart from its purely mechanical properties mentioned before, is to convert starch into sugar. This process, while formerly looked upon as a relatively simple one, has become slightly more complicated as the result of later studies. It is generally believed that by the action of ptyalin, amylase, or diastase, all three names being interchangeably applied to the same ferment, starch is first converted into erythrodextrin, then into achroödextrin, and finally into maltose. Expressed in a chemical equation the process would be:

$$\underset{\text{Soluble starch.}}{10C_{12}H_{20}O_{10}} + 8H_2O = \underset{\text{Maltose.}}{8C_{12}H_{22}O_{11}} + \underset{\text{Achroödextrin.}}{2C_{12}H_{20}O_{10}}$$

On this small amount (20 per cent.) of achroödextrin left unchanged amylase has but little action (Roberts[12]).

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I have said the process is not such a simple one as would at first sight appear, for before being changed into sugar the starch must first be liquefied. Maquenne and Roux (quoted by Roger[8]), in studying the action of malt, found that these two processes are brought about by two distinct ferments, and they believe that starch is composed of two substances: the one, amylocellulose, or amylose, easily converted into sugar, and amylopectin, which gives to the starch paste its consistence. Amylase converts the starch into sugar, while the amylopectin is liquefied by a special ferment, a pectinase. Strangely enough, heating to 80° C. destroys the amylase, but does not affect the pectinase.

Roger has in part confirmed the work of Maquenne and Roux, finding, however, that the salivary amylase is more resistent to heat than is the malt amylase, and that while a high temperature prevents its ferment action, it does not destroy it. He has found an amylopectinase in the saliva, and although he has not been able to isolate the two ferments, he has disassociated the two actions. Which gland is responsible for this interesting phenomenon seems to be uncertain, for Roger has found after bilateral removal of the parotid, submaxillary, and sublingual glands in the rabbit, a saliva rich in pectinase and amylase is secreted. He is inclined to believe that the principal role is to be ascribed to the numerous racemose gland situated on the floor of the mouth.

The action of saliva on other foodstuffs is insignificant. Glycogen, which is analogous in the animal kingdom to starch in the vegetable kingdom, is but slowly converted into sugar. Glucose itself is not attacked in the mouth, but Roger believes that after ingestion of large amounts of cane sugar, the human saliva contains an invertin. A fibrin-digesting ferment in the pig's saliva has been described by Hufner and Munk (Roger), which, according to Munk, is active in either acid or alkaline media.

It is generally believed that the chemical function of saliva is, after all, but slight, and that its action on starch continues only so long as starch remains in the mouth, being soon stopped after entrance into the stomach by the acid gastric juice. Cannon, in 1898, and later in conjunction with Day,[13] has shown that this is not true, that the salivary digestion of starch in the stomach by the saliva

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proceeds uninterruptedly for an hour or two. In 1898 Cannon[13] demonstrated that there is no peristalsis in the cardiac portion of the stomach, the food being held in the tonic grasp of the musculature, whereas the pyloric part of the stomach mixes the food thoroughly with the gastric juices. Even after thirty minutes, when the food in the pyloric region has advanced toward chymification, that in the cardiac end has preserved its original appearance. Moreover, the surface of the material in the cardiac end becomes acid, while the interior of the mass remains unchanged in reaction. His conclusions that salivary digestion in the stomach may proceed for one and one-half hours, or even longer, without interruption by the gastric juice have been corroborated by Oehl, and later by Grützner (quoted by Cannon) by means of frozen sections. As long ago as 1880, von der Velden showed that free hydrochloric acid did not appear for almost an hour after eating breakfast, and for almost two hours after eating a full mid-day meal, so the medium remains favorable for carbohydrate digestion for some time.

Cannon and Day[14] conducted an interesting experiment in cats. They gave the animals carbohydrate food mixed with active saliva, and examined the dried content of pyloric and cardiac portions of the stomach. At the end of one-half hour and at the end of an hour the cardiac portion contained about 80 per cent. more sugar in unit volume than the pyloric end. After an hour the ratio of the sugar percentage in the two parts of the stomach began to approximate unity again, due probably to diffusion of sugar from the fundus into the pyloric end, and to some extent to absorption.

Von Zebrowski[6] states that the digestion of starch at the height of gastric digestion is only exceptional, but that in the end stage ptyalin again becomes active, though in lesser degree than before.

The digestive importance of saliva is closely linked with the thoroughness of the masticatory act. In non-chewing animals, as the bird, and in aquatic mammals, which wet their food by constantly swallowing water, as seals and sables, the parotid glands are rudimentary or entirely absent. On the other hand, in animals living on very dry substances, as hay or forage, the glands are well developed. The functions of the saliva have already been discussed, and it will be readily understood that the proper functioning of the digestive

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fluid depends entirely on mastication. It will be unnecessary to go into the whys and wherefores of chewing our food, for those interested will find in the masterly article of Campbell[15] full reasons. Horace Fletcher, in his works, has presented very striking evidence of the good effects following thorough insalivation of the food.

In this connection I may be permitted to recall the injurious effects noted when the food is bolted. Cannon, in studying the pyloric reflex, found that when hard masses of undigested food are brought to the pyloric sphincter, their presence prolongs the period of pyloric closure. Under the circumstances, the hard food particles are repeatedly swept up to the exit, only to be barred there and shot back through the advancing ring of constriction. After a time, the peristaltic waves are able, by persistent churning, to break up the solid particles of food, "a function performed by the teeth with manifestly greater efficiency than by the soft, gastric mucosa."

From the studies of Cannon, Pawlow, and others, it may be deduced that mastication has very important functions. It initiates secretion of the gastric juice; mixes saliva with the food, so that starch is changed to sugar in the cardiac end of the stomach; prevents bolting of food, so that the hard particles of food need not be comminuted in the pyloric mill, and in this way facilitates gastric digestion.

Certain Aspects of the Pathology of Saliva. The behavior of saliva in diseased conditions has not been sufficiently studied, and the results obtained from its study have not been of much practical and clinical value. Dentists, among whom may be mentioned Michaels, Kirk, Talbot, and Price, have given the subject considerable attention, and have claimed to find semeiological evidence of many diseased states.

As far back as 1866 Mosler[16] made the observation that in typhoid fever there was a suppression of secretion, in icterus no bile appeared in the saliva, while he was never able to find any glucose in the secretion in diabetes. Uffelmann[17] pointed out that certain fever conditions, especially acute fevers, were often associated with acid saliva, also that the sugar-converting power of the saliva decreased with the height of the fever. By far the most important contribution is by Jawein,[18] who made rather extensive studies in a number (thirty-six) of widely varying diseases. He found that in mild febrile con-

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ditions the amount of saliva was increased, but the ferment activity remained unchanged; in severer conditions the amount was considerably diminished and the amylolytic action increased, while in very severe pyrexia saliva was excreted in minimal amounts with diminution of ferment action, both being in direct relation to the severity of the disease. In prolonged asthenic diseases, such as diabetes, nephritis, and Addison's disease, he found the ferment activity often decreased. Jawein's statement that sialorrhea and sialaporia are present in the various anemias, led Hamill[19] to investigate this question more closely, but with negative results.

Michaels[20] and later Kirk[21] have claimed a relationship between the presence of lactic and oxalic acids in the saliva and diathetic states, but much more work must be done along this line before the proper significance of their studies can be determined.

Kyle[22] has attempted to point out a connection between hay fever and changes in the chemistry of the saliva, but his results are so inconclusive that a great deal of research remains to be done before his findings can hope to rank as semeiologically valuable.

Acid saliva has been made a study by Acree and Hinkins,[23] in the course of which research they were led to believe that the saliva is acid in the gland in these cases, but is changed in the mouth to an alkaline reaction. Just how this is brought about they do not state, although they assert positively that it is not through bacterial activity. In all probability an underlying acidosis is the principal cause.

Diminution of Saliva. In 1889 Hutchinson and Hadden (quoted by Roger[8]) described a morbid state which they called aptyalism or xerostomia. They found this in old people, especially women, who suffered with almost total suppression of saliva, and with this exhibited dry mouth, tongue red and raw, painful mastication and deglutition, and difficulty in speech. With the diminution in saliva is often associated diminution of nasal and lacrymal secretions. Aptyalism, although causing the teeth to fall out, is not accompanied by grave disturbances, and is perfectly compatible with existence.

A decreased flow of saliva is seen in morbid states, with increased output of water from kidneys, bowels, etc., as in diabetes. In fever dulling of the nervous system may play a role in decreasing the salivary secretion.

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Certain poisons, as atropine and morphine decrease the amount of saliva.

Loss of saliva from the economy is followed by severe disturbance. Wright (quoted by Hellat[24]) claims to have lost eleven pounds in a week by expectorating 250 grams a day for experimental purposes. Frerichs[24] found himself suffering with pain in the epigastrium and loss of weight after experimenting with saliva, and Pawlow[24] caused dogs to become greatly emaciated by "Scheinfütterung." Bursenius[24] and Ruisch[24] both claim to have restored under-nourished individuals to perfect health by making them swallow their saliva, which they were in the habit of expectorating. Lukjanow[24] says the salivary glands have a not insignificant effect on the general health apart from their ferment action. One cannot deny that besides the saliva which goes into the mouth, the salivary glands give other substances into the lymph and blood; in other words, they probably contribute an internal secretion to the organism.

INCREASE OF SALIVA. Besides the reflexes already mentioned, Roger[8] mentions two others heretofore undescribed. The one, the esophagosalivary reflex, is brought about by mechanical irritation of the esophagus. This is useful clinically, as the increased flow of saliva would tend to dislodge any irritating foreign body located in the esophagus. The other, or the gastrosalivary reflex, is seen when acid is introduced into the stomach, and the sialorrhea called forth may be stopped on giving sodium bicarbonate. This may explain the salivation noted in cases of hyperacidity, and in all probability the function of the increase of saliva is to neutralize the excess of acid present in the stomach.

Sialorrhea is more common than a diminished flow of saliva, and apart from local diseases, such as stomatitis, parotitis, and pharyngitis, and certain drugs, as mercury, there are many nervous conditions associated with salivation. Klippel and Sejas (quoted by Roger[8]) have described a nervous sialorrhea which is apparently associated with nervous hyperexcitability. The spumous liquid seen at the end of an epileptic seizure is well known, and cases of hysteria have bloody saliva, the blood coming direct from the glands (Mathieu, quoted by Roger[8]). Migraine and exophthalmic goitre exhibit sialorrhea, and in tabes dorsalis, a salivary crisis, expressed in hyper-

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secretion, is often seen as an isolated phenomenon or associated with gastric crises. Many other instances may be mentioned, but the above suffice as illustrations from the domain of neurology.

The gynecologist will bear witness to the intimate association of the genital organs to the salivary glands. Uterine trouble is often accompanied by sialorrhea, and in neurotic women there is seen an increased flow of saliva at menstrual periods and at the menopause. Sialorrhea often depends on metritis or some abnormal position of the uterus, and Tamburini (quoted by Roger[8]) claims to have cured a rebellious salivation by fixing a retroflexed uterus. At the beginning of pregnancy ptyalism is very frequent, and some women even diagnosticate their condition by the increased flow of saliva.

An attempt has been made in this paper to review in brief outline the latest work bearing on the salivary secretion. The appended bibliography is not large, but it is all that remained after the more than a hundred references had been studied and their value carefully assayed.

Discussion.

Dr. David Riesman: I want to ask Dr. Goodman if he found anything new in the literature on the subject of potassium sulphocyanid and its significance in the saliva.

Two cases of sialorrhea have come under my observation—one that of a woman in the early stages of pregnancy who consulted me solely on account of the excessive flow of saliva. Without trouble she was able to collect and to bring 300 c.c. of saliva, which was found to be actively amylolytic. The second case was that of a man operated upon by Dr. Stewart for hernia. Immediately after the operation the patient began to be troubled with profuse salivation. For days he had to go around with a towel and basin to gather the saliva that was drooling from his mouth. This saliva was also actively amylolytic.

Dr. Goodman in answer to Dr. Riesman's question: According to the work of de Souza potassium sulphocyanide must be regarded as an excrementitious substance formed from proteid metabolism and is not manufactured by the parotid gland.

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Enlargement of the Hypophysis Cerebri and its Relation to Acromegaly.

BY EDWARD B. KRUMBHAAR, M.D.

(From the Ayer Clinical Laboratory, Pennsylvania Hospital.)

ENLARGEMENTS of the hypophysis are of interest not only on account of the general and localizing symptoms of brain tumor that they produce, but still more on account of their undoubted but hitherto poorly understood connection with such constitutional changes as occur in acromegaly, gigantism, and adiposo-genital degeneration. In the great majority of cases of acromegaly that have come to autopsy, enlargements of one kind or another of the hypophysis have been found (47 out of 49 in Furnivall's[1] sta-

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tistics and 44 out of 48 in Hutchinson's[2]); and yet so many cases of acromegaly with no lesion of the hypophysis, and of enlargement of the hypophysis with no acromegaly, have been reported that no generalization on the connection between the two can as yet be substantiated.

In the following case of a tumor of the hypophysis, the subject was large, with well-developed muscles covered by a considerable layer of fat. He could not be called a giant, and there were no evidences of acromegaly, nor of the various physical signs of adiposogenital degeneration. His physical condition had apparently not changed since he had reached adult life, though the symptoms of brain tumor had become evident only in the past few years. The history of the case is as follows:

William B., aged forty-three years, negro, laborer. Admitted to Pennsylvania Hospital, August 11, 1908, during the service of Dr. Newlin. He died a few hours later. The patient was brought to the hospital by police patrol in an unconscious state, and the history was obtained the next day from his father and his wife.

His mother had died of cancer of the uterus over twenty years ago. His father was living and healthy. He was born in the eighth month of pregnancy, and was weak till he was ten or twelve years old. He had temporary lateral curvature of the spine, which he outgrew. At eighteen he was strong and healthy. He always worked at hard manual labor. He married his present wife ten years ago. She says he was as corpulent and strong then as at present. She had one abortion in the seventh month of pregnancy, and had one child which lived only a few hours. Venereal infection was denied. The patient always drank to excess and smoked tobacco. "He always seemed to suffer in the top part of his head," and has always had headaches since a small boy. These have been worse since he was hit on the head by an iron gate, three years ago. The injury was diagnosticated as fracture of the skull.

Last winter he first noticed attacks of dizziness, nausea, vomiting, and increased headache. The sight of both eyes began to get dim. Lately the attacks have come about once a week. On the day of his admission he had an attack in which he was unable to stand upright or to speak, though he was conscious and evidently understood

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what was said to him. When he arrived in the patrol, he was unconscious and limp. Later he became stiff all over, and died, two hours after admission, of respiratory failure, without regaining consciousness. The urine contained albumin. No physical examination was made.

Autopsy (No. 1126) was performed sixteen hours after death. *Anatomical diagnosis*: Tumor of pituitary body; œdema of brain; acute vegetative mitral endocarditis; acute bronchopneumonia; congestion of lungs, kidneys, intestines, and pancreas; acute splenic tumor; fatty degeneration of liver; chronic mitral and aortic endocarditis; concentric cardiac hypertrophy; chronic adhesive fibrous pleurisy (right side); chronic fibrous orchitis (left side); arteriosclerosis of aorta, innominate and iliac arteries. *Microscopically*, there was also found a chronic interstitial myocarditis and slight chronic diffuse nephritis, and the tumor of the pituitary body was diagnosticated as an adenoma.

The following measurements of the exterior of the body were taken: The body weighs about 195 pounds and measures 175 cm. in length; the circumference of the head, 57.5 cm.; from the symphysis of the chin to the angle of the jaw, 12 cm.; chest, 108.5 cm.; abdomen, 98.5 cm.; from top of the sternum to symphysis of the pubis, 58 cm.; from the tip of the acromion to styloid process of the radius, 62 cm.; circumference of arm, 35 cm.; of forearm, 30 cm.; from styloid process of ulna to tip of forefinger, 19 cm.; from great trochanter to the internal malleolus, 88 cm.; circumference of thigh, 59 cm., calf, 38 cm.; length of foot (tip of great toe), 27.5 cm.

Only the notes on the glands of internal secretion are given in full. This subject will be discussed at more length later on. The various body measurements are also given as proof of the general, relatively symmetrical, good but not excessive development.

The thyroid weighs 32 grams. It is of a normal dark red color, of normal consistency and shape. The isthmus is fairly well developed, being 3.5 cm. long. Microscopically, there is a moderate increase of fibrous tissue throughout the section. The bloodvessels appear slightly more congested than normal, and the acini are for the most part moderately distended with pink-staining colloid material, though some are small and empty. In many the lining epithelium is unattached, lying free in the lumen of the acinus or embedded in the

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colloid material. The epithelium is cuboidal, with a pale-staining, vesicular nucleus and pale granular protoplasm. The interstitial tissue is diffusely increased between the acini, and in many places has an almost hyaline appearance. Large thickened trabeculæ are also found, also often showing hyaline degeneration. In some places, numerous minute capillaries filled with red blood-cells surround the acini; in others, small vessels are found embedded in the large trabeculæ described. No acini reach a diameter of more than 1 or 2 mm. The capsule is normal.

Four parathyroids are found, three on the right side. They are reddish pink, and the small vessels appeared dilated. Two are the size of very small peas, one about the size of the head of a pin. The thyroid arteries are stiff and rigid. Microscopically, all the glandules appear congested, the epithelial columns alternating regularly in many places with distended capillaries. In one, a large vessel which runs through the middle of the glandule is also distended with red blood cells. The epithelial cells have a round or oval, fairly deep, regular staining nucleus and a pale or transparent protoplasm, the cell membrane in many places being alone visible. The capillaries are in very intimate relationship with the cells, the smaller ones apparently separated by the thin vessel wall only. In other places small groups of capillaries are surrounded by a relatively large amount of connective tissue. Two of the glandules have a fairly definite capsule, in the others the exact limit of the gland cannot be determined, as the epithelial columns push out between lobules of fat or occur isolated in fat or connective tissue, at some distance from the main body. About the two glands that are encapsulated there is a considerable amount of these apparently aberrant epithelial cells. They occur in strands or irregular groups, and are in the same intimate relation with numerous capillaries. The cells themselves have the same type of nucleus, but the protoplasm stains much darker.

The right testicle is larger than the left and contains a small amount of clear, straw-colored fluid in the tunica albuginea. The testicles weigh together 42 grams. They are apparently normal and the tissue unravels readily, though the left is somewhat redder. The tissue appears slightly shrivelled and the cortex is increased. Microscopically, the seminiferous tubules are for the most part normal, and

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the interstitial tissue is not increased. In some places, however, there are areas in which the tubules are completely replaced by a dense, coarse, fibrous tissue, poor in cells. This is limited to the outline of each individual tubule, and is quite easily distinguished from the surrounding loose interstitial tissue. These fibrosed tubules occur, for the most part, in masses; but the process can be found occasionally extending its way between normal tubules and occasionally normal tubules are found in the midst of the fibrosed ones. This fibrosis is found to be caused by a thickening of the capsules of the tubules, and various grades can be found between slight thickening and a complete fibrosis. The interstitial cells in these areas, as elsewhere through the organ, are not diminished in size or number. Coarse, yellow granules are visible in less than half of them, the protoplasm in the remainder taking the eosin stain faintly and being finely granular. Spermatoblasts, spermatids, and spermatozoa of the seminiferous tubules are normal, though many of the basement cells have been detached from the basement membrane. The bloodvessels throughout the organ are normal. The capsule is thick and in places has undergone hyaline degeneration.

The adrenals weigh 12.7 grams and are apparently normal. Microscopically, the epithelial cells of both adrenals, especially of the zona fasciculata, are extensively vacuolated. The nature of these vacuoles was not determined, but they are probably the modified fat that is usually found in these cells. The cells of the zona glomerulosa take the eosin stain more deeply, though in practically all minute vacuoles can be found. The nuclei are small, round, and highly chromatic. In the zona fasciculata, the protoplasm is almost all replaced by large or small vacuoles, in many cases only the cell membrane being visible. The nuclei are either small, round, and chromatic, or larger, vesicular, and reticulated. The latter appear to be more numerous in the more extensively vacuolated cells. The pigmented cells of the chromaffin system are numerous and prominent, though the pigment is more of a diffuse yellow coloration of the protoplasm than definite, coarse granules. Immediately outside the normal capsule, in the sulci made by convolutions of the gland, are collections of cells that closely resemble the epithelial cells of the adrenal gland. They are fairly large, with considerable finely granu-

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lar protoplasm and a small, round, highly chromatic nucleus. (The nature of these cells was not determined.)

BRAIN. On removing the calvarium, which is normal and not thickened and shows no signs of fracture, numerous small bleeding points appear on the dura. The brain tissue appears normal, though somewhat soggy. The lateral ventricles are distended with fluid. On removing the brain, the pituitary fossa is found to be much enlarged and to be filled with a tumor-like mass about the size of a crab-apple. The fossa is shallow and has a much wider diameter than normal. The posterior clinoid processes are obliterated. Further examination is postponed until the brain is hardened. On the surface of the pia, which is everywhere smooth and glistening, there are numerous minute black dots, which also appear upon the pia covering the pons and medulla. The internal carotid artery appears thickened and the walls do not collapse. The cerebellum, pons, and medulla are apparently normal. The brain weighs 1240 grams.

After hardening, horizontal sections are made. In the right hemisphere, about 1 cm. below the dome in the parietal region, are two small cavities about the size of small marbles, which do not connect with the lateral ventricles. They involve only the white matter. One sulcus, however, approaches close to them, and its gray matter in the vicinity of the cavities is thinner than elsewhere. Beneath these cavities the brain substance is much softer than in the corresponding parts of the opposing hemisphere. This softening involves the lenticular nucleus and the external capsule. The last section goes through the middle of the largest lobule of the tumor, showing it red and fleshy in appearance and rather soft and friable, with a granular surface. It intrudes mostly under the right hemisphere, but also somewhat under the left. On the falx cerebri, between the frontal lobes, the dura shows two irregular areas of bone formation about 1 cm. in diameter. Microscopic examination of the small cavities shows a gradual rarefaction of the cerebral tissue, with a gradual disappearance of nuclei near the ragged edge of the cavity. No signs of any inflammation or hemorrhage are found about them.

TUMOR OF THE PITUITARY BODY. The tumor occupying the sella turcica is reddish gray, soft, and almost fluctuating. It shows some dark red areas and dilated vessels. On section, it is found to

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have a similar hemisphere about twice the size of the other, which projects up into the right frontal lobe. On its anterior surface is a smaller lobule the size of a cherry. The two hemispheres are constricted about the middle by the optic chiasm anteriorly and by the optic tracts posteriorly. Until the pia was dissected, only the half below this constricting girdle was visible. The cut section of this tumor mass bulges, is moist, and of a reddish flesh color. The optic chiasm and tracts are much stretched and attenuated by pressure from the tumor. On separating the loose connective tissue which joins them to the tumor, it can be lifted out of its socket except for a long, thin, delicate pedicle joining it to the base of the brain. No sign of a normal pituitary body can be found. Where the tumor has pressed on the right inferior frontal lobe it is much softened, depressed, and fluctuates.

Sections from all parts of this tumor show a very cellular tissue that varies but little in different parts. Remnants of both portions of the normal gland are found stretched about it like an envelope. The tumor is bounded by a fairly thick, regular capsule, which in no place appears to be infiltrated by the cells of the mass of the tissue. These cells have a round, reticulated, fairly deep-staining nucleus (about 6 to 10 microns in diameter). Almost all are surrounded by a fair amount of pale-staining, homogeneous protoplasm. In some this is so delicate and pale that it is barely visible. Nothing approaching chromophile granules is demonstrable by ordinary or special stains. A small proportion of cells have a small, round, highly chromatic nucleus and either no visible protoplasm or considerable homogeneous protoplasm, the latter appearing not unlike a plasma cell. Frozen sections and teased specimens show the same character of cell. The interstitial tissue is very scanty for the most part, showing as extremely fine, delicate blue fibers (Mallory's stain) or occasionally short sections of fairly small trabeculæ. Special stains for neuroglia fibers (Weigert and Mallory), myelin sheaths (Weigert), and elastic fibers (Verhoeff's) fail to show their presence. Small capillaries are fairly numerous in some sections (especially those from the superior and posterior portions), but are very sparse in other parts. A very few larger vessels are found in the tissue, but even in these only a few scattered elastic fibers can be found.

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Surrounding parts of the superior and posterior lobules of the tumor like a capsule is a narrow strip of tissue, never more than 1 mm. in thickness, that more nearly resembles the structure of the normal glandular portion of the hypophysis, and probably here represents its remnants. The cells are arranged in columns, parallel to the capsule of the tumor, separated by a delicate reticulum. These columns represent the compressed and elongated acini. The cells are of two kinds, one with a large, pale, vesicular nucleus, and varying amounts of pale protoplasm; the other with a smaller, more highly chromatic nucleus, and more and deeply stained protoplasm. These approach the type of chromophile cells, but no definite chromophilic granules can be made out.

Adjacent to this narrow strip, representing the normal glandular portion, lies a circumscribed piece of loose connective tissue (1 x 4 mm.) that has exactly the appearance of the posterior lobe of a normal hypophysis. It is definitely encapsulated, has the characteristic loose reticulated structure enclosing numerous large, pale nuclei. At the junction with the attenuated anterior portion there is an ingrowth of epithelial cells similar to those of the anterior portion, just as is seen in the majority of normal pituitary bodies. Small bloodvessels are fairly numerous.

We therefore find in an extremely well-developed adult, who had been weak as a child, but normal since puberty, and the same size for at least ten years, a tumor of the hypophysis, which had given localizing symptoms for certainly six months, and probably two or three years. Nothing more definite could be elicited about the cerebral symptoms in spite of repeated questioning, as both father and wife, though willing, were not very intelligent. It is impossible, therefore, to fix the age of the tumor, or to exclude it as the cause of the small degree of macrosomia that existed.

The tumor has been classified as an adenoma of the glandular portion, on account of its benign appearance macroscopically and the character of the cells microscopically. It was surrounded everywhere by a capsule and showed no tendency to invade the surrounding tissue, the damage it caused to surrounding structures being by pressure only. It is not considered a glandular hyperplasia or struma of the anterior portion, because the remains of the normal gland were

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found stretched about the tumor. The sparsity of interstitial tissue and lack of the normal alveolar arrangement of the anterior portion of the hypophysis also point against this. The cells, though differing from those of a normal gland, certainly resemble them much more closely than they do any type of sarcoma cell; and furthermore the encapsulated condition of the tumor and its evidently slow growth argue against sarcoma. The differential diagnosis between hyperplasia, adenoma, adenocarcinoma, and sarcoma of the hypophysis appears to be, in many cases, very difficult or impossible to make. Even a superficial examination of the literature will show numerous cases where a conscientious writer, who has carefully examined his material, was unable to reach a diagnosis, or where one author disputes as probably incorrect the diagnosis of another.[3]

No significant changes were present in the organs of internal secretion, with the exception of the marked congestion of the parathyroids. The localized fibrosed areas in the testicle are paralleled by the arteriosclerosis and sclerotic changes in some of the other organs. The thyroid, though small, was not enough so to be called abnormal; neither did the slight increase of interstitial tissue appear of great significance. The number and prominence of the chromaffin cells of the adrenal is interesting.

The respectability of a known antiquity attaches to enlargements of the hypophysis, for as far back as 1679, Theophilus Bonetus[4] described what was evidently a serous cyst of the hypophysis, as follows:

" § 1. *Capitis dolor ab abscessu seroso, natibus cerebri et infundibulo adhærente.*

"A girl of twelve, of a phlegmatic and dull temperament, suffered for four months with a severe continuous headache. When called to her care, I found her quite without fever, but rejecting all food. She lived for many days on sugared water only. She complained only of pain over the coronal sutures. All remedies were in vain. No swelling or redness was present. Finally, death put an end to her miseries and pains.

"On opening the head, everything was found, beyond expectation, well formed and without corruption. I had expected to find pus, as a little before death the right eye had emitted some purulent fluid.

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But when we despaired of ascertaining the cause, the surgeon, wishing to demonstrate to his pupils the rete mirabilis and other parts, broke with his fingers an abscess which was adherent to the folds and infundibulum of the cerebrum, from which clear water flowed with force to the extent of two pounds, as if gushing from a fountain." (In the above case, the enormous cyst, the modern equivalent of serous abscess, if attached to the infundibulum, evidently arose in the hypophysis. The dull, phlegmatic temperament is interesting as a possible evidence of myxedema, which has been found to have some connection with lesions of the hypophysis.)

Shortly after Marie[5] had given acromegaly its name, and had demonstrated that it was a "special morbid entity," the connection between it and lesions of the hypophysis was made apparent. In his original paper, however, which was a description of two cases observed during life, this connection was naturally not suspected. It is interesting, however, to note that both patients suffered from continued headache, and that the second not only had suddenly become blind, but, as seen in the photograph accompanying the text, had an external strabismus of the right eye. That these symptons might indicate an intracranial tumor apparently escaped the author's attention. By 1889, Marie[6] had already collected 18 cases, and in all three in which complete autopsies were performed, enlargements of the hypophysis were found. Many different lesions have been found to cause enlargement of the gland—simple hypertrophy or struma, adenoma, carcinoma, sarcoma, cysts, teratoma, lipoma (Bruns[7]), tuberculosis, gumma, hematoma (Hippel[8]), echinococcus cyst (Hippel[8]). The first five of these, however, constitute the vast majority of recorded examples; and in many cases it was impossible to make an absolute diagnosis of the character of the tumor.

In attempting to explain the coincidence of hypophyseal enlargement and acromegaly or gigantism, many theories have been propounded: first, that advocated by Marie, that a deficient hypophyseal secretion (*i. e.*, injury to the gland by the tumor) caused the metabolic changes that resulted in acromegaly. Massalongo[9] took the opposite stand to Marie. He claimed that the hypophysis and thymus, normally active only until puberty, in acromegalics retained their function into adult life, their persistent secretion causing the trophic

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changes. But as Cagnetto[10] well observes, in order to explain the appearance of acromegaly late in life, he must either assume that the tissues were extraordinarily resistant or that the dominant glands suddenly resumed activity. An outgrowth of Massalongo's theory was that of Tamburini,[11] that the somatic changes were caused by an excessive hypophyseal secretion, either if hypertrophied or replaced by a tumor. This latter sounds improbable, but would be no more extraordinary than the bile- and colloid-secreting carcinomatous nodules on the skull secondary to carcinomata of the liver and thyroid* (Schmidt[12]). It is interesting to note here Woods Hutchinson's[2] autopsy on a dwarf, in which the hypophysis was found much shrunken and sclerotic.

The division of the cells of the anterior lobe into two classes—the pale, chief, or chromophobe cells and the granular, chromophile cells—furnishes Tamburini with another prop to his theory. Benda[13] had previously shown with special stains that all grades could be found between the two classes, so that it was easy to assume that they were the same cell in different stages of activity. He[3] later found four cases of acromegaly, all of which showed hypophyseal tumors and three with numerous chromophile cells. In all four the remains of both lobes of the normal gland were found. They therefore support Tamburini's theory that acromegaly is due to a hyperfunction of the gland, and this is evidenced by the presence of chromophile cells. Unfortunately for this theory, however, Cagnetto[14] has lately reported two cases of acromegaly with a tumor of the anterior portion of the hypophysis, in which the chromophile cells were, if anything, sparser than normal, and a third case of hypophyseal hypertrophy, in which the chromophile cells were much increased, but in which acromegaly was absent. The present case, therefore, is in accord with this theory, as an example of a tumor of the hypophysis, not consisting of chromophile cells, in which no signs of any constitutional somatic changes were present, and, therefore, no changes would be expected to be found in the glands of internal secretion.

The possible influence of the posterior portion of the gland must

*See also Stadelmann, Deut. med. Woch., 1901, No. 32, p. 536.

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not be overlooked; and it may easily be found that hypertrophy or obliteration of this portion of the gland has something to do with the production of acromegaly. That it has some function cannot be doubted; for instance, its power to raise the blood pressure has been well established, and very recently Pemberton and Sweet[15] have found that extracts of the posterior portion have, in common with extracts of suprarenal glands, the property of inhibiting pancreatic secretion. In the present case, it will be remembered that, in addition to the attenuated anterior lobe, the posterior lobe was preserved in apparently normal condition. Hippel,[8] however, states that no tumor of the posterior portion has ever been reported.

Still another explanation is offered in the so-called endogenetic theory (advocated by Strümpell[16]), which claims that both acromegaly and hypophyseal enlargement are coördinated symptoms of some unknown metabolic change, and that in given cases either symptom may be absent. The hypophyseal enlargement is thought to have no causal relation to the somatic changes but to be merely a concomitant symptom. The recent experimental and operative work that has been done on the hypophysis throws an interesting light on this view. In Vienna, in the past year, three hypophyseal tumors have been removed by the nasal route (two cases of adiposogenital degeneration,[17] and one of acromegaly[18]), in all of which the patient not only recovered from the operation, but experienced within a few months a marked improvement in symptoms. Experimentally hypophysotoxic serum,[19] secured by injecting extracts of the anterior lobe, has been found to produce skeletal changes (deformities, epiphyseal swellings) that suggest a similarity to acromegaly. These facts, at least, tend to establish the hypophyseal changes as causal.

In the interaction of the glands of internal secretion, on which so much experimental work has lately been done, the hypophysis is found to take an active part.[20] It is found to hypertrophy after castration, thyroidectomy, or extirpation of the adrenals. Injection of hypophyseal extract is said to cause hyperfunction and hypertrophy of the adrenals; while injection of the thyroid extract lessens the function and size of the hypophysis. In myxedema and exophthalmic goitre changes are found in the hypophysis as well as in the thyroid. It is, therefore, a possible supposition that in the few cases of acro-

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megaly or gigantism thus far reported, in which the hypophysis is not involved, the abnormal stimulus has been supplied by one of the other glands of internal secretion.

In this connection it will be remembered that in the present case no significant anatomical changes were found in any of the other glands of internal secretion, though the possibility of a perverted functioning cannot be excluded.

The frequent concurrence of diabetes and acromegaly is significant in this connection; especially as in late years the tendency has been more and more to regard certain cases of diabetes as the possible result of lesions of other organs than the pancreas (*e. g.*, the adrenal glands or the chromaffin system in general). It might, therefore, easily be imagined how the same abnormal grouping of glands of internal secretion that caused acromegaly might also cause diabetes. Eleven years ago Hansemann[21] found 12 cases of diabetes in 97 of acromegaly, and in fact Strümpell uses this as one of the arguments in favor of his endogenetic theory.

CONCLUSIONS. 1. The present case is one of an apparently benign cellular tumor of the anterior lobe of the hypophysis with preservation of both anterior and posterior lobes of the normal gland, causing local pressure symptoms, but no constitutional changes such as acromegaly, gigantism, or adiposogenital degeneration. No significant anatomical changes were found in any of the other glands of internal secretion.

2. The cells of the tumor resemble the chromophobe cells of the anterior lobe (were certainly not chromophile cells); so that the present case is in accord with the theory that hypophyseal enlargement does not cause acromegaly, unless there is also an increase of chromophile cells.

3. Each theory hitherto advocated to explain the connection between hypophyseal enlargement and the above constitutional changes has been met with so many contradictory cases that none can be accepted as convincing, although that of Tamburini and Benda at present appears the most probable.

4. The association of the two conditions, however, is so nearly constant that it is fair to assume that some such connection probably exists. A consideration of the various ways in which the organs of

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internal secretion are known to interact suggests as a possible hypothesis that those cases of acromegaly or hypophysis tumor that are contradictory may be explained by some compensatory action on the part of one or more of these glands of internal secretion.

Discussion.

Dr. D. J. McCarthy: I think that every well-studied contribution to a subject like the physiology and pathology of the hypophysis is very welcome; because, if there is one subject that is poorly understood, it is this one. That this gland is a very important structure, there is no question. The mere fact that we have such varied disturbances as those mentioned, and that the removal of the pituitary body in dogs is followed by death, points to its significance. After very extensive study of the pituitary, after examining a large number of sections, and reviewing the literature of the subject, I find that I am as much at sea as to the pathology and physiology of the pituitary body as I was some years ago. I have a collection of four or five tumors and two cysts of the pituitary. Two of the tumors were associated with adipose conditions. I should like to take issue with Dr. Krumbhaar in his statement that the glands have not been studied. A careful study was made by me of a case of adiposis dolorosa in association with faulty development of the genitalia. A collection of an extensive group of cases has shown that, besides this condition of adiposis dolorosa associated with tumors of the pituitary, there is a condition called adiposis cerebralis. The former is a chronic condition of adiposis, whereas adiposis cerebralis refers to an extensive diffusion of fat developing with a brain tumor. In the discussion of these cases it was suggested that there may have been an interchange of function between the ovaries and testicles and the pituitary body—that the pituitary was concerned with the metabolism and growth of the structural economy up to the period of adult life, and that the testicle and possibly the ovary, by an internal secretion from the interstitial cells, was concerned in the diffusion of fat; but that, when these organs took up their function of generation, the pituitary took on their function of fat-production. In the

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cases in which this was studied there were tumors of the pituitary and adiposis cerebralis.

DR. J. H. W. RHEIN: I am now studying a case of tumor of the pituitary region, probably of the pituitary body, that resembles Dr. Krumbhaar's case in some respects. In my case, however, the tumor was much larger than his, and was also multiple.

The patient was a man of middle age who showed no signs of acromegaly or gigantism. The symptoms consisted of general convulsions, total blindness, and persistent headache.

The largest of the tumors was the size of my fist, and there were two or three others, smaller in size. These tumors were circumscribed, and did not infiltrate the brain tissue. The largest tumor forced its way upward, compressing the anterior lobes of the cerebrum, and pushing the lower floor of the anterior horns of the lateral ventricles upward so that there was only a small layer of brain tissue covering the tumor. Below, the tumor caused necrosis of the bones forming the base of the skull. The optic chiasm was stretched over the tumor, and was flattened out, resembling a ribbon.

All these tumors and various parts of the large tumor were studied microscopically, but no tissue that could be said to be the pituitary body could be found. The tumor was made up of a congregation of cells which somewhat resembled those of the normal pituitary body. These cells were surrounded by alveoli, and in places were found to push their way beyond the limits of these. The tumors were probably cancerous.

A further study of these cells by staining for the chromophilic and chromophobic cells is now being made, and a report of the results of this study, together with a full report of the case, will be made to this society at a future date.

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January 28, 1909.

Card Specimens Presented February 11, 1909.

DR. ARTHUR V. MEIGS and DR. C. B. FARR:
Heart Showing an Extreme Degree of Aortic and Mitral Stenosis.

Interesting on account of long duration. Patient, an unmarried female, died at 64. Valvular disease was first recognized by Dr. Meigs' father when patient was 9 years of age.

At autopsy the heart was found moderately enlarged; there was simple hypertrophy of the left ventricle; dilatation of the left auricle; hypertrophy and dilatation of the right ventricle. The aortic cusps were rigid, partly calcareous and adherent at their margins, leaving a narrow chink only. The mitral leaflets showed similar changes, a "button-hole" opening only remaining. The liver showed passive congestion, the kidneys were sclerotic and the spleen indurated.

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DR. JOHN FUNKE:

(1) *A Lymphosarcoma Involving the Omentum.*

This specimen was taken from a patient twenty-eight years old, who was taken ill July 4, 1908, but who was not compelled to go to bed until the latter part of the same month and who died at the end of September. The patient had an enormously distended abdomen; but on tapping no fluid could be obtained.

At autopsy a mass involving the omentum principally, was found in the abdominal cavity. The lowermost portion of the omentum contained several large masses, which were not detected during life and many smaller ones disseminated throughout the entire structure. The retroperitoneal lymph nodes were greatly involved. The pelvis was almost completely filled by a large mass compressing the rectum along the course of which structure there were also smaller nodes. Along the brim of the pelvis were many smaller masses. These tumors were all similar in structure. They were greyish-pink, rather firm, encapsulated, cut readily and the incised surfaces were granular and moist.

(2) *Heart with Congenital Malformation.*

The heart is from a child fifteen months old. It shows a marked stenosis of the pulmonary orifice, with a persistent truncus arteriosus which arises from the right and the left ventricles. There is a persistent ductus arteriosus and foramen ovale. The pulmonary artery between the ductus arteriosus and the origin is very small.

(3) *Specimens Showing the Production of Edema on Gelatin by the Action of Acid.*

Dr. Coplin has a few specimens which he would like to show but was unable to be present. They illustrate the production of edema as a result of the action of acids. In one specimen, formic acid was placed along a line, and the gelatin then treated with water and in four minutes wheals developed. By introducing a needle, moistened with formic acid, into living skin similar wheals result. Another interesting feature of the experiment is the fact that, if after the action of some fixative agent, such as bichromate of potas-

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sium upon the gelatin, the formic acid be introduced, no edema results. Accordingly the gelatin was treated with bichromate of potassium, then with formic acid and finally with water with the result that one can barely see the outline of the area treated with formic acid. The edema was also prevented by the action of fuchsin. These specimens illustrate the theory of edema resulting from the chemical changes in the colloids as pointed out by Emil Fischer.

DR. R. S. LAVENSON:

(1) *Sacculated Aneurysm of the Arch of the Aorta;* (2) *Cylindrical Aneurysm of the Descending Aorta.*

This specimen consists of a large sacculated aneurysm involving the arch of the aorta from just above the aortic leaflets to just below the point of origin of the left subclavian artery. At the latter point, the aorta assumes its normal caliber, which it retains for about a centimeter, after which a second dilatation, cylindrical in form, commences. This second dilatation extends from this point throughout the entire thoracic portion of the aorta. The aneurysm of the arch has eroded the sternum anteriorly, and the vertebræ posteriorly. It is interesting to note the extent to which the attachment of the pericardium to the root of the aorta has been raised by the dilatation of the latter. I think that reconstructing the aneurysm, as was done in this case, instead of exposing the interior of the sac, as is usually done, permits of a much more satisfactory demonstration and a much clearer interpretation of the anatomical peculiarities of the aneurysm.

DR. H. S. WIEDER:

A Ruptured Double Saccular Aneurysm of the Arch of the Aorta.

This aneurysm apparently gave no symptoms previous to sudden death. The patient suffered from temporary aphasia and permanent right-sided hemiplegia of two years' duration. In the notes made at an examination on admission, the only reference to the heart is a slight increase in rate. There was no increase in the dulness, and no murmur over the chest.

At autopsy this double saccular aneurysm was found. The first

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sac is six centimeters above the origin of the aorta, this being the only vessel communicating with it. It is five centimeters in breadth. At the lower portion there is a minute opening through which it has ruptured into the pericardial cavity only. There is another sac a short distance further up seven and a half centimeters in breadth, twelve centimeters from the aortic valve. From this the innominate left carotid and left subclavian arteries arise. The left carotid and left subclavian arteries are obliterated by organized blood clots. There must have been a perfect collateral circulation not to have produced clinical signs or symptoms. The innominate artery enters into the sac but is apparently closed like a ball valve by the large clot in the sac.

Card Specimens Presented March 11, 1909.

DR. JOHN SPEESE:

Carcinoma of the Thyroid.

The tumor of the thyroid was removed by Dr. C. H. Frazier, a diagnosis of malignancy having been made. The patient, aged 11, had a large tumor of the gland which had been gradually enlarging for six years until it reached the size of an apple, occupying chiefly, the right side of the neck. At the operation, both lobes were found to be enlarged and both were removed. The microscopic examination showed a simple hypertrophy in the left one, and in the right a carcinomatous degeneration of a papillary-cyst-adenoma. The patient lived several days after the operation but gradually grew weaker from post-operative shock from which he did not recover.

DR. DAVID RIESMAN:

Specimens from a case of Chronic Pulmonary and Acute Miliary Tuberculosis, Large Fatty Liver, Perihepatitis, and Jaundice.

The specimens came from the body of a woman, 24 years of age, who was brought to the Philadelphia Hospital in a delirious condition. Examination on admission showed great enlargement of the liver, with a friction sound just below the right costal arch. The lower abdomen was distended, tense and tympanitic; jaundice was

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present; on the legs there were a number of petechial hemorrhages. Nothing was detected over the lungs except a few rales at the left base; over the heart a soft, mitral systolic murmur was heard. Pelvic examination was negative. The leukocytes varied from 4000 to 6000. The Widal test and blood culture were negative; the sputum did not contain tubercle bacilli.

A diagnosis of miliary tuberculosis, enlargement of the liver, and localized peritonitis was made. At the autopsy these conditions were found; in addition there were several small tuberculous cavities in the lungs. The heart valves were normal. The miliary tuberculosis was most marked in the peritoneum which was studded with minute gray nodules; these were evidently very young, showing giant cells but no trace of caseation. The liver was enormously enlarged, soft, of a butter yellow color, and greased the knife on section. The right lobe was covered with a fibrinous exudate. On microscopic examination the liver cells were found to be completely replaced by fat. The brain was not examined.

The interesting points in the case are the co-existence of fatty liver with jaundice, a rare combination. In symptomatology the case bore a strong resemblance to acute yellow atrophy, except that the liver was large. The phrase "acute yellow hypertrophy," coined by Rolleston, is quite applicable to the case. The patient had been addicted to alcoholism. That and the tuberculosis probably account for the fatty liver, but the pathogensis of fatty liver is obscure and there may have been other factors.

DR. GEORGE FETTEROLF:

A Rare Anomaly of the Kidney.

The specimen shown was a right kidney, obtained from the body of a colored woman of unknown age in the University of Pennsylvania Dissecting Room. The left kidney was normal in size, situation, construction and relations.

The specimen measured 9 x 6 x 3 cm. and weighed 115 gm. It lay in the right iliac fossa, extending from the lower border of the second lumbar vertebra to the lower border of the fifth and was not movable.

In the centre of the anterior surface was a large roughened area

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surrounded by a broad margin of kidney cortex, which with the rest of the kidney surface was smooth and easily denuded of its capsule. The ureter began at the lower inner part of this rough area and followed its margin in the form of a letter C, receiving six calices in its course. It left the gland at the middle of the anterior inner surface and thence was normal. The main renal vessels passed downward and outward behind the gland and curved around the lower outer portion to enter the renal substance through the periphery of the rough area. Small additional vessels passed through a notch on the mesial surface. Associated anomalies were an elongated right lobe of the liver and the emptying of the right ovarian vein into the renal.

The cause of the condition might be a rotation of 180° through the transverse axis, caused by the overgrowth of the right hepatic lobe, and an outward rotation through the vertical axis, due possibly to traction exerted by the main renal vessels.

DR. W. M. L. COPLIN:

Arm Showing Lesion Presenting the Gross Appearances of Gastric Ulcer.

About a month ago, in demonstrating to the class the colloid theory of edema, I injected into my forearm a number of substances capable of producing urticaria; conspicuous among these was formic acid. Most of the lesions disappeared as artificial bee-stings usually do. Two developed necrosis and went on to small ulcers. One of these without treatment of any kind, soon healed leaving no scar. In one there had been a considerable excess of formic acid and the necrosis extended down to the muscle. As the spot was 0.8 cm. in diameter, I concluded to try the application of artificial gastric juice. I applied this at interrupted periods. The ulcer remained large for about twelve days. Its floor was perfectly clean, showing healthy fascia and muscle; the edges became rounded and elevated but not undermined. Four or five days ago contraction began, but it is not yet healed, and though almost six weeks have elapsed, the floor of the ulcer shows no reparative effort. For two or three days after the application of the artificial gastric juice, it

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showed the clean, smooth, bright floor of a typical gastric ulcer, and I think that at the present time one can see the induration and margins typical in gastric ulcer. The artificial gastric juice consisted of two per cent. pepsin dissolved in two-tenths per cent. aqueous dilution of hydrochloric acid. The acid alone did not clean up the floor of the ulcer.

DR. A. G. ELLIS:

A Specimen of Tuberculous Ulcers of the Stomach.

This specimen I obtained at autopsy from a woman of eighty-five who had ulcerative tuberculosis of both lungs, and numerous ulcers of the colon and the ileum. In the stomach, on the greater curvature, about midway between the pylorus and the cardia, is a row of eight ulcers, some more than a centimeter in diameter. In addition there are four tubercles that appear on the verge of ulcer formation.

Spreads made from scrapings of the ulcers contain numerous tubercle bacilli.

DR. SIDNEY J. REPPLIER:

Cystadenocarcinoma of the Thyroid.

From Mrs. G. W., age thirty-six, operated on by Dr. Wharton at the Presbyterian Hospital. Macroscopically, the tumor, which was removed in pieces, shows numerous cysts ranging from pin-head to pea size, filled with a dark-colored fluid. Microscopically the tumor proved to be a papillary cystadenocarcinoma.

An Experimental Study of Joint Affections Induced by the Typhoid Bacillus.

BY A. G. ELLIS, M.D.

(From the Laboratories of the Jefferson Medical College Hospital.)

AFFECTIONS of the joints, though not a rarity, are not excessively common during the course of typhoid fever. Despite their relative infrequency, certain clinical and pathological characters combine

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to render them of special interest. Among these points are the varied physical and bacteriological nature of the effusion, spontaneous dislocation, and the usually favorable, or at least non-fatal, course of the complication. This last fact largely accounts for our unsatisfactory knowledge concerning the pathology of these lesions.

Literature on both the clinical and experimental aspects of the subject is not conclusive. One point that was formerly disputed should now be regarded as definitely settled, namely, that the typhoid bacillus, even in the joints, is a pus-producing organism. This statement is not vitiated by the finding in some instances of sterile fluid in those cavities during the course of what clinically appeared to be a certain typhoid arthritis, as such finding is readily explained by experimental cases; the typhoid bacillus after producing the lesion dies out. Further, the cases in which the typhoid bacillus has been found in the pus of infected joints, although bacteriological examination has too seldom been made, are sufficiently numerous to demonstrate the pyogenic properties of that organism.

Johnson[1] describes a case occurring in a woman aged twenty-five years. During convalescence from typhoid fever her right wrist became swollen and painful. Pus aspirated from the joint contained a pure culture of the typhoid bacillus. Martin and Robertson[2] record a case in a man aged thirty-four years. Pus aspirated from the fluctuating tumor about the wrist-joint showed a pure culture of the typhoid bacillus. A second aspiration two weeks later showed only a small quantity of bloody pus.

Spontaneous dislocation of the hip is one of the most puzzling complications of typhoid fever. Ardisson[3] found that this disease was responsible for 33 of the 84 reported cases of this lesion; the other most frequent causes were polyarticular rheumatism with 23, and scarlet fever with 11 cases. Ardisson discusses at length the three leading theories of the cause of luxation, namely, (1) accumulation of fluid in the joint; (2) tissue proliferation in the acetabulum; and (3) the muscular theory. As before stated, this condition almost always terminates favorably, and the pathology is therefore but little understood.

Graff[4] says that little is known of the mechanism of spontaneous luxation. Petit believed that an acute hydrarthrosis distends the

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capsule and ligaments. Verneuil and Reclus held that muscle pull plays a role, and Hunter that the joint is dilated by an effusion of pus. From numerous Röntgen-ray studies of spontaneous dislocation after typhoid, puerperal sepsis, and acute osteomyelitis, Graff believes that in all cases the upper part of the acetabulum flattens, in part disappears, no actual destructive process, however, being demonstrable. The effusion in the joint is serofibrinous, and without capsular dilatation leads to inflammatory softening of the upper acetabular rim. Pressure upon this by the head of the femur leads to atrophy and flattening, so that the head slowly moves above and posterior.

Freeman[5] reports a case of spontaneous dislocation of the hip in a girl aged ten years. He says that most writers agree that the prime factor in dislocation is overdistention of the joint by fluid. The ligamentum teres is not necessarily ruptured, Moore having experimentally demonstrated that it may be sufficiently elongated by an intra-articular effusion to allow of complete dislocation without loss of continuity.

Kummer[6] says, regarding the content of the joint in cases of spontaneous dislocation of the hip in connection with acute infectious diseases, that in 29 cases in which the presence of arthritis was known before dislocation occurred, 22 were serous or serofibrinous and 3 purulent. Kummer adds two typhoid cases of his own, but does not give the bacteriology of any of the 51 cases of spontaneous dislocation of which he presents brief notes.

I have found but two reports that are at all definite upon the pathology of spontaneous dislocation, and one of these is valuable largely for its negative findings. Both were old operative cases, and hence throw no light on the early stages of the joint affection.

Rawdon[7] describes a case occurring in a girl aged eight years. He first saw the patient in June, the history being that during an attack of typhoid fever which lasted from February to May she complained of pain in the right thigh and knee, but not in the hip; later, deformity of the thigh developed. Rawdon operated, removing the head of the femur. The head showed no notable absorption. Synovial membrane was not demonstrable. The cartilage was in general intact, showing only a little absorption around the circumference at its junction with the neck. The bony structure of the head

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and neck was absolutely normal and the surrounding tissues were notably healthy.

Hübener[8] reports the case of a girl, aged fourteen years, admitted to the hospital April 1. The preceding September she had an attack of typhoid fever, with a short recurrence on the thirty-first day. Two months afterward the right hip became affected. The foot and knee previously swelled, but soon subsided under treatment. Pain in the hip kept the child in bed for a time, and then the hip was found to be out of joint. A skiagraph showed dislocation of the femur, the acetabulum being still well formed with a sharp border. The head of the femur was loose at the epiphyseal line. Operation revealed the acetabulum empty and covered by slight masses of granulation tissue. The head of the femur was free and lay behind and above the acetabulum embedded in a moderate amount of granulation tissue. The head of the bone and the new tissue were removed. In this tissue were typhoid bacilli. The patient died, but autopsy was not permitted. Hübener believes there was exudate in the joint before dislocation occurred.

As with the clinical, so with the experimental studies of typhoid joint affections. But little work along this line has been done, and the findings are therefore not conclusive. Investigations have been made chiefly upon rabbits, as, though these animals are quite refractory to the typhoid bacillus, they are in many ways the most suitable for experimental work.

Orloff[9] found that the effusion in joints after the injection of typhoid bacilli may be serous, seropurulent, or purulent, the first and second being most frequent. He injected 13 rabbits in the knee-joint, at the same time injecting into the opposite joint sterile water or bouillon, according as he had employed an emulsion of agar growth or bouillon culture of the bacillus. One-half to 1 c.c. of the material was used. The joints were studied after periods of time ranging from fifteen hours to thirty-seven days.

Twenty-four hours after injection the joints were swollen and the subcutaneous tissues edematous. In some instances the whole lower leg showed edema, this probably being partly due to the 5 per cent. carbolic acid solution used to disinfect the leg. Removal of the skin during the first twelve to twenty-four hours revealed dilated vessels,

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this also being true of the synovial membrane; at times there was actual hemorrhage. In the cases investigated later the hemorrhage was slight. In the joints, especially the upper recess, was a thick, tough, more or less cloudy fluid not seldom in large quantities. Joints examined later contained opaque, white, moderately hard, kernel-like masses, and the fluid was more turbid and seropurulent in type. In from twenty-four to thirty-seven days the fluid was still more thick and adherent to the synovial membrane. In the fluid of the first day, also later, were pus cells in small or large numbers. Typhoid bacilli were present during the first two days; after eight or nine days they were with one exception absent; in that one instance they were found on the thirteenth day. In the control knees the injected fluid was entirely absorbed.

Orloff also injected typhoid bacilli into muscles, under periosteum, etc., in order to investigate the pus-producing properties of that organism. His *resume* concerning the joint lesions was that there was produced a seropurulent, frequently thick, mucus-like exudate. He afterward repeated his experiments, using sterilized cultures instead of living bacilli and obtained the same results, though the reaction was weaker. One of his conclusions was that the suppurative processes developing during typhoid fever, when the pus contains exclusively typhoid bacilli, are due to that organism alone, and are not to be regarded as the consequence of a mixed infection of typhoid bacilli and pus cocci.

Arcoles[10] injected bouillon cultures of the typhoid bacillus into joints or veins of 5 young rabbits. He produced suppurative arthritis by direct injection into joints or by injuring joints after injecting bacilli into a vein. Bacilli were found in the effusion in the affected joints.

Florange[11] believes that typhoid arthritis comes often from lesions of the neighboring bones. The typhoid bacillus is constantly in the bone marrow of those suffering from typhoid fever, and its pyogenic powers are well known. It may then invade a joint from the bone, and thus be a propagation from an osseous infection. Most often, he believes, there is not a typhoid infection, properly so called, of the joint, but simply an irritation of the neighboring parts caused by an inflamed epiphysis; the articular effusion is sterile. The epiphyseal

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osteitis is here the principal lesion, the arthritis being secondary and less important. Florange's contention is partially supported by the experiments of Klemm,[13] who injected 8 rabbits in an ear vein and afterward found in the bone marrow of 5 of them a pure culture of the typhoid bacillus, though arthritis was not induced. Pus was found in none of the cases.

My object in carrying out the experimental study here recorded was to add to our knowledge of the action of the typhoid bacillus in joints, especially, if possible, after causing their presence in those cavities by means other than direct injection.

The first set of experiments was made by using a bouillon growth of a stock culture of the typhoid bacillus of uncertain virulence; 1 c.c. of a twenty-four, forty-eight, seventy-two hour or older growth was injected directly into a knee-joint and those structures examined at various periods later. In all of this series the skin over the site of injection was first washed with soap and water and then with a 5 per cent. carbolic acid solution. When the joints were examined, spreads and inoculations were made from the joint content, and in most instances tissue was fixed and finally studied in stained sections. The results can best be given in brief protocols of the individual animals. Spontaneous death as it occurred in some of the rabbits, with the exception of the one due to pneumonia, in these series of cases, was apparently due to the lesion produced or to the conditions of captivity; at least, no anatomical changes pointing to other more definite causes were found.

Rabbit 1. One c.c. twenty-four hour bouillon culture typhoid bacillus injected in knee-joint. Next day, joint red and much swollen; second day, moderately swollen; third day, essentially normal. (These early phenomena were common to all the animals of this series.) Rabbit chloroformed on seventh day. Joint moderately distended, motion less free than on opposite side. In joint is 0.5 c.c. thick, tenacious, grayish fluid. Synovial membrane lustreless. Microscopically, fluid contains numerous cells, 53 per cent. polynuclear, 47 per cent. mononuclear. Many of the latter are evidently endothelial cells, and some of them contain polynuclear leukocytes in varied stages of disintegration. Sections through the cartilage of the femur show a covering of granular acidophilic detritus and leukocytes, but no erosion. Inoculations from the joint were sterile.

Rabbit 2. One c.c. forty-eight hour bouillon culture typhoid bacillus injected in knee-joint. Animal killed on the tenth day. Joint slightly swollen and motion less free. Practically no free fluid in joint cavity. Spreads from scrapings contain many

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cells, mononuclear 87 per cent., polynuclear 13 per cent. Tissues show no lesion. Inoculations from the joint remained sterile.

Rabbit 3. One c.c. seventy-two hour bouillon culture typhoid bacillus injected in knee-joint. Animal found dead on tenth day, the joint having been gnawed open by other rabbits. In the spreads from the content are great numbers of cells, approximately 65 per cent. mononuclear, though degeneration is too advanced for an accurate count. Synovial membrane shows engorgement of vessels and infiltration by mononuclear cells; no erosion.

Rabbit 4. One c.c. seventy-two hour bouillon culture typhoid bacillus injected in knee-joint. On the second day an unsuccessful attempt was made to withdraw fluid from the joint by means of a hypodermic needle. Rabbit chloroformed on the fifty-eighth day. No erosion of tissues. Inoculations gave growth of unidentified cocci.

Rabbit 5. One c.c. six day bouillon culture typhoid bacillus injected in knee-joint. Rabbit found dead on the thirty-third day. Joint not swollen, and contains small quantity of tenacious, almost clear fluid. Vessels around joint slightly injected. No erosions. In spreads a few cells, all mononuclear, well preserved. Inoculations sterile.

Rabbit 6. One c.c. forty-eight hour bouillon culture typhoid bacillus injected in knee-joint. Rabbit killed on fourth day. Joint is moderately swollen and motion less free than on opposite side. Interior of joint essentially the same as in Rabbit 1. Spreads contain many cells, 88 per cent. of which are polynuclear. No erosions.

Rabbit 7. One c.c. forty-eight hour bouillon culture typhoid bacillus injected in knee-joint. Rabbit found dead on the sixteenth day. Apparently only normal amount of synovial fluid within joint. Spreads contain very few cells, many so degenerated that accurate differential count cannot be made. Tissues of joint show no definite lesion. Inoculation sterile.

Rabbit 8. One c.c. six day bouillon culture typhoid bacillus injected in knee-joint. Animal killed on forty-fifth day. No evident gross lesions. Few cells in spreads, all mononuclear and well preserved. Tissues show no lesion. Inoculation from joint sterile.

Rabbit 9. One c.c. twenty-four hour bouillon culture typhoid bacillus injected in knee-joint after it was roughly manipulated for one minute. Rabbit found dead on the sixth day. Considerable thick, grayish fluid in joint. Synovial membrane grayish. In spreads are many cells, polynuclears 72 per cent. Tissues show no lesions. Inoculations gave pure culture typhoid bacillus.

Rabbit 10. One c.c. twenty-four hour bouillon culture typhoid bacillus injected in knee-joint, which was then scraped with point of needle. Rabbit found dead next day. No free fluid in joint, but a scanty, tenacious, almost clear material adheres to synovial membrane. Latter structure ecchymotic, where injured by needle. In spreads are enormous numbers of cells, 98 per cent. polynuclears. Inoculation from joint gave pure culture of typhoid bacillus.

The results of these experiments indicated that the bacilli employed were not sufficiently virulent to produce noteworthy lesions in the joint tissues, although an inflammatory exudate appeared in the cavity. They did show that at first the cells in the exudate were practically

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all polynuclear leukocytes, these after a few days giving way to mononuclears. The latter were nearly all of the large or hyaline variety of lymphocyte, or were endothelial cells, very few lymphoid cells being found. The endothelial cells were phagocytic for polynuclear leukocytes.

In the 8 cases in which inoculations were made from the joint the typhoid bacillus was found twice, after the lapse of one and six days respectively. Five others were sterile at the end of seven, ten, sixteen, thirty-three, and forty-five days. One only, No. 4, contained bacteria other than the typhoid bacillus; the presence of cocci in this case is fully explained by the fact that on the second day an attempt was made to aspirate the joint.

In the second series of experiments the typhoid bacilli employed were increased in virulence by repeated passage through guinea-pigs until one-tenth loop intraperitoneally was sufficient to kill a 200-gram pig within eighteen hours. Emulsions of twenty-four hour agar growth in sterile water were used for injection. In order to avoid the irritating effect of carbolic acid solution, the skin over the joint was prepared by simply washing with alcohol. That this was sufficient precaution is shown by the fact that contamination not once occurred, inoculations from the joints always giving a pure culture of the typhoid bacillus or remaining sterile. The typhoid bacillus was identified during its preparation and in the cultures from joints by the fermentation, Conradi-Drigalski, and agglutination tests.

I began this series with the attempt to induce lesions of joints in some way other than by direct injection into them of bacilli. With this aim several methods were employed, only to be abandoned because of anatomical or operative difficulties or because of lack of results. The ten experiments in this group are as follows:

Rabbit 11. One-tenth loop typhoid bacilli injected into left carotid artery and double ligature applied. Animal died in thirteen days from double pneumonia and pleuritis. No joint lesions.

Rabbit 12. Injected same as No. 11. Rabbit apparently sound at end of fifty-seven days.

Rabbits 13 and 14. One-tenth loop typhoid bacilli injected into ear vein. On the following day the knee-joints of each were roughly manipulated by pressing, twisting, etc. At end of one week the joints showed no lesion.

Rabbit 15. One-tenth loop typhoid bacilli injected into ear vein. Two days later the large artery to right hip-joint was ligated. After a few days the animal began

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emaciating, and on the sixteenth day, when on the point of dying, was killed. Both hip-joints appeared the same, that is, normal. Spreads from the content of each were identical. Inoculations from right-hip-joint were sterile.

Rabbit 16. Injection and ligation same as in No. 15. Animal killed on fortieth day. Both hip-joints normal.

Rabbit 17. One-tenth loop typhoid bacilli injected into ear vein. Next day large vein from right hip-joint ligated. Rabbit found dead on eighteenth day. Both hip-joints normal. In spreads a few more cells in those from the right. Inoculations from right hip sterile.

Rabbit 18. One-tenth loop typhoid bacilli injected into ear vein. Next day right femoral artery ligated. Rabbit found dead on the twenty-eighth day. Vessel proved to be occluded at point of ligature. No detectable difference in the joints or other parts of the two legs.

Rabbit 19. One-tenth loop typhoid bacilli injected into ear vein. Next day femoral vein ligated. After two days leg became considerably edematous. Later this largely disappeared and general emaciation began. Rabbit found dead on twelfth day. Joints on right side no different from those on left. Spreads from both the same. Inoculations from right knee-joint sterile.

In rabbits 13 to 19 inclusive, therefore, attempts were made, after the injection of bacilli into the circulation, to create by trauma, or by interference with the circulation, a *locus minoris resistentia* in one or more of the joints, with the hope that in this way the bacilli might be induced to colonize therein. As seen from the protocols, this object was not attained. In one animal an attempt was then made to throw the bacilli into the circulation at a site nearer the joint than is the ear.

Rabbit 20. Femoral artery of right leg exposed and attempt made to inject bacilli into the vessel, as was done in the carotid of Nos. 1 and 2. The caliber of the artery proved too small for the blood to flow by the needle when the latter was introduced, consequently this project had to be abandoned and the artery ligated.

The idea of causing localization of bacilli in joints by way of the circulation was then abandoned and the remainder of the experiments confined to injecting bacilli directly into the joints. To produce a condition comparable to that in human beings with typhoid fever, if the bacilli lived, injections were made into the veins of four rabbits at different periods before the joints were inoculated.

Rabbit 21. One-tenth loop typhoid bacilli injected into ear vein. One week later one loop bacilli injected into knee-joint. On following day the joint was red and greatly swollen. Animal killed on seventh day when nearly dead. The injected joint was loose, that is, permitted unusual latitude of motion, especially in the lateral direction. In the joint was a small quantity of soft, yellowish, granular material. This was in connection by small openings through the capsule with two periarthritic abscesses. Spreads of the joint content show many endothelial cells, most of which contain numer-

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ous vacuoles. In addition are enormous numbers of leukocytes, at least three-fourths of which appear to be polynuclear, though many are so degenerated that their type cannot be determined. A few threads of fibrin are present. Inoculations from the joint remained sterile.

Rabbit 22. Injected in ear and joint same as No. 21. Animal killed on eighth day when nearly dead. Injected joint very loose; can be fully flexed readily and bent laterally to angle of 50 degrees. The quadriceps tendon can be easily thrown out of its groove by manipulating the joint; this cannot be done with the opposite leg. In the joint is a considerable quantity of yellow, moderately tenacious fluid. Over the surfaces of the joint and extending upward for some distance in the sheath of the quadriceps tendon is a yellowish, friable deposit resembling degenerated fibrin. In the posterior recess of the joint is 1 c.c. of thick, yellow pus. The interarticular ligaments are destroyed, presenting only as indefinite masses of reddish yellow debris covered by the described exudate. The semilunar and articular cartilages are not appreciably affected, either in color or consistency. In spreads from the joint content are many leukocytes, 95 per cent. of which are polynuclears. In many only the nucleus remains. There is a moderate number of endothelial cells, with more or less fatty degeneration of the protoplasm. Inoculations from the joint gave a pure culture of the typhoid bacillus.

Rabbit 23. One-tenth loop typhoid bacilli injected in ear vein, and four days later one loop in third joint of hind leg. Animal found dead on thirteenth day. Pronounced serofibrinous pleuritis, and pericarditis. Joint contains small quantity of tenacious, turbid fluid, in which are endothelial cells and moderate number of leukocytes, about half of the latter polynuclears.

Rabbit 24. One-tenth loop typhoid bacilli injected in ear vein, and three days later one loop in third joint of hind leg. Animal found dead on forty-seventh day, the joint differing in nowise from the corresponding one on the opposite side.

The results in rabbits 21 and 22 show clearly that a suppurative arthritis can be induced by the typhoid bacillus. Further, and this is of special importance in connection with the problem of spontaneous luxation, is the fact that motion in the affected joints was of much greater latitude than is normal. This in No. 22 is readily explained by the destruction of the interarticular ligaments; in the other, changes in the capsule and surrounding tissues, with possibly some yielding of the ligaments, must be held accountable. That a suppurative arthritis is present as the underlying lesion in all, or even any, of the cases of spontaneous luxation in human beings cannot be said; in truth, the clinical history of most of them would indicate that such was not the case. Notwithstanding this, the fact that the typhoid bacillus can occasion such destruction of articular tissues as was found in Case 22 is of importance. This case is further of interest in that the typhoid bacillus was still living in the joint on the eighth day after injection.

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In the remaining experiments of this series, typhoid bacilli were injected directly into the knee-joint, this being the only expedient employed.

Rabbit 25. One-half loop typhoid bacilli injected in knee-joint about 4 P.M. Animal found dead next morning with no evidence of reaction in the joint. Spreads from the joint content contain numerous bacilli and occasional endothelial cells. Inoculation from the joint gave a pure culture of the typhoid bacillus.

Rabbit 26. One loop typhoid bacilli injected in knee-joint. Next day, joint red and greatly swollen. Animal killed on fourth day. Joint much swollen, containing a thick, tenacious, yellow fluid. In spreads are many cells, 93 per cent. polynuclears, most of remainder endothelial cells. Many of both types show extensive degenerative changes. A few of the polynuclears contain bacilli. The joint tissues show no erosion. Inoculation from joint gave pure culture of the typhoid bacillus.

Rabbit 27. One-half loop typhoid bacilli injected in knee-joint. Next day, joint red, swollen, and tender. Third day, rabbit sick, with profuse diarrhea. On sixth day was emaciated but fairly lively; was killed. In the swollen joint is considerable turbid fluid. This is especially true of the posterior part, from which a mass of cheesy material extends into the surrounding tissues. Articular surfaces and ligaments show no gross lesion. Spreads contain enormous numbers of leukocytes, 95 per cent. polynuclears, and many endothelial cells, the latter showing extensive fatty degeneration. Inoculation from joint proved sterile.

A piece of the muscle bordering the joint was prepared and sectioned. Sections including the joint capsule and attached tissue show on the former a mass of exudate consisting of leukocytes, fibrin, and red cells. A few endothelial cells are also present. The outer portions are thickly infiltrated by mononuclear cells, chiefly large with vesicular nuclei, among which are a few polynuclears. The muscle has for the larger part almost or entirely lost its cross striation. The fibers are in many instances partially hyaline and show pronounced longitudinal furrowing or actual separation into fibrils. At points the bloodvessels are surrounded by mantles of mononuclear cells.

Rabbit 28. One loop typhoid bacilli injected in knee-joint. Next day joint much swollen and red. Animal found dead on eighth day, the joint being greatly swollen. In it is a large quantity of thick, yellow fluid exactly resembling pus as found in human beings. This permeates the entire joint, being beneath the semilunar cartilages. Adherent to the articular surfaces is a quite thick layer of grayish-yellow material undoubtedly fibrinous in character. The interarticular ligaments are covered by the exudate and the superficial portions are necrotic. The periarticular tissues are also infiltrated by pus. The articular cartilages are not eroded. Spreads from the joint content contain a great deal of fibrin and numerous leukocytes, many of which show pronounced degeneration; the great majority of those still identifiable are polynuclears. A few degenerated endothelial cells are present, as are also occasional bacilli. Inoculation from the joint contents, though only a few colonies grew, proved a pure culture of the typhoid bacillis.

Portions of the quadriceps tendon and of the adjoining muscle were fixed and sectioned. Microscopically the muscle is largely necrotic, these areas being closely packed with leukocytes. Most of these are polynuclears, though bordering the necrotic masses mononuclears predominate. The outlying portions of muscle not yet necrotic have

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lost their transverse striation. Beween the fibers are many mononuclear cells and also numerous polynuclear eosinophiles. The inner surface of the tendon is also partly necrotic. In the remainder the fibers are separated by mononuclear leukocytes, and here, as in the muscle, are polynuclear eosinophiles.

Rabbit 29. One-half loop typhoid bacilli injected in knee-joint, which became red, swollen, and tender. Animal found dead on eighth day. The joint is swollen, but its motion not freer than that of the one opposite. In the joint is a small quantity of thick, yellow fluid, which in the posterior pocket becomes caseous. The anterior interarticular ligament is covered by exudate and the superficial portion is slightly necrotic. Just posterior to the insertion of this ligament to the tibia is an area of erosion 2 mm. in diameter, in which jagged bone is exposed.* Spreads of the joint content contain many leukocytes, a large number degenerated, but the great majority polynuclear. Endothelial cells, some showing fatty degeneration, are also present. Inoculations were not made.

Sections through the joint capsule and adherent tissues are densely infiltrated by mononuclear cells, many with large, partly vesicular nuclei. At points are masses of fibrin. The quadriceps muscle shows distention of bloodvessels, collections of mononuclear leukocytes in the interstitial tissue, and hyaline degeneration of some of the fibers.

Rabbit 30. One-half loop typhoid bacilli injected in knee-joint, which became red, swollen, and tender. Animal found dead on the eighth day. The joint is very loose, especially permitting excessive lateral motion. In the joint is a large amount of grayish yellow fluid. The anterior interarticular ligament is reduced to a few thread-like masses of reddish material covered by exudate. The internal borders of the semilunar cartilages are eroded and thinned. The articular cartilages are intact. Spreads of the joint fluid contain many leukocytes, 95 per cent. polynuclears, showing but little degeneration, a moderate number of fatty endothelial cells, and numerous threads of fibrin. Inoculations were not made. Sections from the quadriceps muscle show extensive infiltration by mononuclear leukocytes, particularly in the vicinity of vessels. The muscle shows pronounced granular degeneration.

Rabbit 31. One-third loop typhoid bacilli injected in knee-joint. Animal found dead on eighth day. Joint is swollen but not loose. In the joint is yellowish gray exudate. The capsule anteriorly and the quadriceps muscle extending over and along the tendon are largely necrotic. The interarticular ligaments are covered by exudate, but not otherwise appreciably affected. Spreads show essentially the same as in No. 30. Inoculations from joint sterile. Sections through the quadriceps muscle well above the exudate show at the tendon insertion a perivascular round-cell infiltration. Many of the fibers have lost their transverse striation and stain less deeply than do those of normal muscle.

Rabbit 32. One-third loop typhoid bacilli injected in knee-joint. Animal found dead on tenth day. In the greatly swollen joint is a large quantity of yellowish exudate. The interarticular ligaments, semilunar, and articular cartilages show no gross lesions. In spreads of the exudate is a great deal of fibrin. The cells, though both poly- and mononuclear can be recognized, are too much degenerated to permit definite statements

* Bone from this and other cases in which that structure was involved, or at least kept, for investigation, was accidentally destroyed by fire, and, therefore, microscopic studies of it could not be made.

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regarding their percentages. Inoculation from the joint gave a pure culture of the typhoid bacillus.

Rabbit 33. One-third loop typhoid bacilli injected in knee-joint. Animal found dead on eleventh day. The joint is moderately swollen. Vessels of fascia around and for some distance above the joint are markedly infected. The joint capsule is also infected and at points anteriorly is much softened and easily torn. In the joint is a small quantity of yellowish fluid, and in the posterior recess a collection of yellow, granular material. There is no erosion of ligaments or cartilages. In spreads of the joint fluid is a moderate number of leukocytes, many degenerated, the majority present being polynuclears. Inoculations from the joint gave a pure culture of the typhoid bacillus. Sections from the quadriceps muscle show slight granular degeneration of that structure.

Rabbit 34. One loop typhoid bacilli injected in knee-joint. Animal killed on twelfth day. In the joint, which permits freer motion than that on the opposite side, is a small quantity of yellow tenacious material. Extending into the surrounding tissues from posterior portion of joint is a cavity containing 1 c.c. thick yellow pus. In spreads of the joint fluid are a great number of leukocytes, most of which are markedly degenerated, but the majority are polynuclear in type. Inoculations from the joint proved sterile.

Sections from the muscles bounding the joint show in areas atrophy, but most prominent is hyaline degeneration, which here is very extensive. Entire fibers, in some instances several adjoining ones, have lost all structure and appear as a hyaline material stained very slightly by eosin. Such areas are widespread through the sections. Small areas of necrosis are also present, confined to the fibers alone. Some of the necrotic material stains very deeply by hematoxylin, suggesting the probability of calcareous deposits. Between these necrotic muscle fibers the interstitial tissue is very densely infiltrated by leukocytes, the majority mononuclear. In some of the sections the hyaline degeneration is very prominent and necrosis and leukocytic infiltration slight or entirely lacking.

Rabbit 35. One-third loop typhoid bacilli injected in knee-joint. Animal found dead on fourteenth day. Joint swollen with yellow discoloration above and below. The capsule is grayish yellow and soft. In the joint is a small quantity of yellowish fluid with considerable granular material in the posterior part. The interarticular ligaments are covered with exudate but not eroded. Spreads of the joint fluid contain many degenerated leukocytes, a few endothelial cells, and threads of fibrin. Inoculations from the joint were sterile.

Rabbit 36. One-third loop typhoid bacilli injected in knee-joint. Animal found dead on fourteenth day. In the greatly swollen joint is a small quantity of yellow, tenacious fluid. Between the interarticular ligaments and extending laterally, the head of the tibia is bared and eroded over an area 0.5 cm. in diameter, presenting a rough spiculated surface. The capsule is partly necrotic; the interarticular ligaments and joint cartilages are not eroded. Spreads from the joint fluid contain many leukocytes, a few fibrin threads, and a number of greatly degenerated endothelial cells. Inoculations from the joint were sterile. Sections of the muscles bordering the joint show necrosis and leukocytic infiltration as described under No. 34.

Rabbit 37. One loop typhoid bacilli injected in knee-joint. Animal found dead on sixteenth day. In the swollen joint is a moderate quantity of quite thick, yellow fluid. Beneath the semilunar cartilages is a thin layer of fibrinous exudate. In the middle of the head of the tibia, extending from the anterior margin to the interarticular

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ligament and to a small extent over the articular surfaces, is an almost circular area 1 cm. in diameter, in which the bone is bared of its covering and is carious and jagged. From this point the anterior portion of the capsular ligament is necrotic and opens into an abscess which extends under the tendon and to the surrounding tissues. The capsule is also destroyed posteriorly, and the joint cavity here connects with the surrounding abscess. On one of the articular facets of the femur the articular cartilage is superficially eroded over an area 3 by 8 mm. in extent. In spreads from the joint content are a few partly degenerated endothelial cells and an enormous number of leukocytes, 90 per cent. of which are still recognizable as polynuclears. Inoculations from the joint proved sterile.

Summary of the results in the 13 rabbits, Nos. 25 to 37 inclusive, in which direct injection of typhoid bacilli into a joint was the method employed:

In all of the 12 animals which survived a sufficient length of time, a seropurulent or purulent exudate appeared in the joint. In 3 instances there was more or less extensive necrosis of interarticular ligaments. In one there was erosion of the semilunar cartilages. In 3 cases there was destruction of the overlying soft parts and erosion of the articular surface of bone, in each instance the head of the tibia being affected. In 3 cases the muscles bordering the joint showed hyaline degeneration, accompanied or not by areas of necrosis. Inoculations were made from the joint content in 11 of the 13 cases. The typhoid bacillus in pure culture was recovered in 5 instances, after the lapse of one, four, eight, ten, and eleven days respectively. The exudate was sterile in 6 cases, at the end of six, eight, twelve, fourteen, and sixteen days.

In order to verify Orloff's findings as regards the effect of dead bacilli in the joint, I used this material in two experiments. The source of the bacilli employed was guinea-pig 19, the same as that of the organism employed for many of the knee injections already described, hence of equal virulence. The suspension of bacilli was placed before injection for one hour in an oven at 60° C., inoculations made from this suspension at the time of injection proved it to be sterile.

Rabbit 38. One loop typhoid bacilli killed by heating for one hour at 60° C. injected in knee-joint. Next day the joint was red, swollen, and tender; second day, less swollen; third day, normal in size, and color. Animal found dead on the eighth day. The injected joint macroscopically is exactly like the corresponding one of the opposite side. Spreads from the fluid contain a few well-preserved endothelial cells.

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Rabbit 39. Injected same as No. 38. Next day the joint was red, swollen, almost as much as those in which living bacilli were used, and tender. Second day, was less swollen; third day, normal in appearance. Animal found dead on twenty-fifth day. Knee-joints on the two sides absolutely alike.

These two experiments are, of course, insufficient upon which to base conclusions, but the results in my cases are so opposed to those of Orloff as to be noteworthy. He obtained the same effect, except in lesser degree, from killed as from living bacteria. What my two animals would have shown had the joints been examined during the quite violent, but temporary, reaction of the first day or two after the injection is problematical, but Orloff's statement was based on a comparison with his other series, which included periods of time up to thirty-seven days.

Since cases of spontaneous luxation as a feature of typhoid joint affections in human beings are limited to the hip, I attempted, finally, for the sake of better comparison, to induce lesions in that joint instead of in the knee, in rabbits.

Rabbits 40 to 46 inclusive. Attempted injection of typhoid bacilli into hip-joint. Owing to the depth of the joint and its anatomical structure, the capsule was not penetrated by the needle in any of the seven cases. The bacilli were deposited in the tissues overlying the joint or in the neighboring muscles.

These animals all died in from four to fourteen days, presumably from the effects of abscesses or local necroses which developed at the site of injection. The muscles bordering these lesions show in stained sections hyaline degeneration and necrosis as already described in connection with a number of the knee cases. In one instance, in addition to these lesions, the bordering muscle shows quite marked increase of connective tissue, amounting to a distinct productive interstitial myositis.

In general the experiments here described show clearly that the typhoid bacillus is capable of seriously damaging and even destroying the various elements entering into the formation of joints. Collectively, all the component parts of those structures—synovial membrane, interarticular ligaments, semilunar cartilages, articular cartilages, bone, the joint capsule—and the surrounding tissues, including the muscle, were thus affected. Certain of these points, to the best of

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my knowledge, had not previously been demonstrated, and they consequently throw some light on those phases of the pathology of this affection.

Just how far it is safe to apply these findings in animals to the interpretation of typhoid joint affections in human beings is difficult to say. I believe we are justified in considering that all the destructive effects here enumerated are at least possible in human joints. There at once arises the objection that the bacilli experimentally were injected directly into the joints, while in man they enter those structures, if they are present, directly or indirectly by way of the blood stream. This, however, I think, is not an insuperable objection. When the bacillus colonizes and multiplies in the joint its effects must be much the same whatever the portal of entry, providing, of course, that preceding trauma does not play too large a role. While trauma is inflicted by injection in experimental work, the puncturing of the capsule by a fine needle is not a great injury. As before stated, contamination by other bacteria did not occur in a single instance of simple injection.

My study adds but little that is definite concerning our knowledge of spontaneous dislocation, as this complication did not occur in any of the experiments. In truth, reasoning from the cases in man, it was not to be expected, since attempts to produce infection of the hip-joint were not successful. Generally speaking, the results show how dislocation would be favored by the partial or entire destruction of interarticular ligaments and the joint capsule. In one case, No. 22, these structural changes permitted such excessive motion in the joint that dislocation was not at all a remote possibility.

Finally, the outcome of this study suggests at least two points that might be worthy of consideration in further research upon the subject. First, the employment of larger animals, as hares, or even monkeys, in which bacilli could be introduced directly into arteries near the joints. Second, the preparation of typhoid bacilli by growth upon culture media to which were added increasing amounts of the serum of that species of animal to be employed, thus enabling the bacteria to survive for a greater length of time after introduction into those animals.

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Discussion.

Dr. H. M. L. Coplin: One of the important facts shown in this study is the demonstration of peri-articular changes and of alterations in the joint ligaments when bacilli could no longer be demonstrated in the joint fluids. In many cases of typhoid joints and so-called typhoid arthritis, the joint-fluid is found to be sterile; it may be that in these cases an auto-sterilization occurs. Possibly the toxins, endocellular or diffusible, give rise to the peri-articular changes, which, in turn, lead to relaxation of the affected joints and possibly to dislocation. I think that it is a phase of the problem that previous to Dr. Ellis' work has not been approached in an experimental manner.

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The Pathogenesis of Spontaneous Cerebral Hemorrhage.

BY A. G. ELLIS, M.D.,

(From the Pathologico-Anatomical Institute, Prof. Ludwig Pick, Prosector, of the Städtisches Krankenhaus Friedrichshain, Berlin, Germany.)

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1. LITERATURE. The pathology of cerebral hemorrhage has been, for scores of years, a fruitful subject of discussion. Chiefly

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since 1840 there has accumulated an extensive literature, a complete review of which would be beyond the scope of this paper. The monograph of Löwenfeld contains an excellent brief summary of the various findings and the theories advanced previous to the year 1886. The citations without accredited source in the short historical review which is here presented are taken from that book; to it the reader is referred for a fuller discussion of the subject and for further references. Many of the studies reported before that year, as indeed that of Löwenfeld himself, were made by such methods that instructive comparison between the results thus obtained and the findings detailed in this paper can hardly be drawn; the conclusions reached by those writers must, however, be considered.

Brunner (cited by Bonnet, 1700) first observed disease of intracerebral vessels. Morgagni (1761) stated that rupture of these vessels was a consequence of their widening, whereby the walls became thinned. Baillie (1794) held that liability to rupture was increased by the deposit between the vessel coats of bony or earthy material, which diminished their contractility and distensibility. Rochoux (1814) described hemorrhagic perivascular softening which led to extensive hemorrhages by depriving the vessels of their support. In 1844 Rokitansky emphasized the part played by atheromatous and aneurysmal changes in cerebral vessels. Bennet and Bruch (1846) described the presence of granules of fat between the media and adventitia as a pathological condition of the arteries in apoplectic subjects. In the same year Kölliker and Hasse reported finding ball- and pear-shaped ectasias of capillaries and veins.

In 1849 both Kölliker and Pestalozzi spoke of aneurysma spuria on the smallest cerebral arteries, meaning by that term effusion of blood beneath the raised adventitia. Paget, in 1850, observed, in addition to fat accumulation in the adventitia, fatty degeneration of the muscularis of arteries and of the middle coat of veins in three cases of cerebral hemorrhage, and also in the brains of other subjects; he therefore looked upon this degeneration as a frequent occurrence in people above middle age.

Virchow, in a general discussion of aneurysms, said he had often seen the dissecting form (or the aneurysm spurium of Kölliker and Pestalozzi) in brains from apoplectic subjects. None of these writers detected rupture of the inner and middle coats of a vessel

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as a means whereby blood gained access to the space between the latter and the adventitia, although Kölliker described fatty degeneration of both intima and media. Virchow described also what Cruveilhier had observed without recognizing their significance (miliary aneurysms) as ampullar ectasias in which all coats of the vessel took part, without demonstrable structural changes either where they formed the vessel itself or the wall of the aneurysm. Virchow's statement that the outer coat of an artery can imbibe water and become raised to form great sac-like spaces the same as when filled with blood, and also that dissecting aneurysms can be artificially produced by pressing a coverglass upon a mounted vessel, emphasizes the unreliability of these older observations because of the technique employed.

Moosheer (1854) mentioned the presence of dissecting aneurysms on veins as well as upon arteries. He regarded these formations as being closely associated with fatty degeneration of the vessels because this process furnishes a condition favorable to rupture of the two inner coats. Gull (1859) appears to have been the first to find in a hemorrhagic focus a ruptured miliary aneurysm as the source of the bleeding. Eulenberg, in discussing the influence upon cerebral hemorrhage of hypertrophy of the heart and degeneration of arteries, says that in the great majority of cases degeneration of the large and small cerebral arteries is the predisposing cause. On the smallest arteries this change is largely passive, extending from the media as a fatty metamorphosis or simple atrophy. The majority of his 42 cases were not studied microscopically. Bastian (1867) reported miliary aneurysms in two cases, and Paulicki, in the same year, noticed many spindle, globular, or hour-glass dilatations of small vessels.

In 1868 appeared the epoch-making communication of Charcot and Bouchard, who were the first to emphasize the frequency and importance of what they denominated miliary aneurysms; as will be noted from this brief historic review, however, similar formations had already been seen by a number of observers. Charcot and Bouchard reported 60 cases of cerebral apoplexy, in all of which these aneurysms, from two to hundreds in each brain, were found; the rupture of these formations was regarded as the only source of the hemorrhage. These aneurysms were described as visible to the

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naked eye, small globular or fusiform masses from 0.2 to 1 millimeter in diameter, on vessels of 0.03 to 0.25 millimeter. They were regarded as the result of a periarteritis, diffuse in type, which extended inward and caused, or at least was followed by, atrophy of the media. The intima showed only proliferation of the nuclei, or was entirely unchanged. The muscle coat was completely lacking in the aneurysms, their walls being only of adventitia and intima; these two layers were so closely fused as to lose their demarcation.

The technique employed by Charcot was to place the brains in frequently renewed water until small masses of tissue, still attached by vascular filaments, floated to the surface. These were searched for aneurysms, which, when found, were examined in the fresh state by feeble magnification. If study of the contained blood was desired, the aneurysms were ruptured by pressing upon the coverglass. This investigation of Charcot and Bouchard, which was finally extended to 84 cases, was of great value in directing attention to the frequency and importance of these miliary aneurysms in the gross pathology of cerebral hemorrhage. As a contribution to the microscopic anatomy of those formations, or of the vessels upon which they were situated, the technique made it of relatively little interest.

Weiss found many spindle and saccular aneurysms in the brain of a man aged sixty-two years. He agreed with Charcot and Bouchard's findings, except that in the wall of the aneurysm he observed also the lesions of endarteritis. The entire atrophy of the muscularis on a circumscribed place appeared to him the positive factor in aneurysm formation, whether this atrophy was due to sclerosis of the intima or to periarteritis. His microscopic studies were likewise made upon fresh specimens.

Roth found only one of eight cases lacking in aneurysms. He asserted that those structures were due to amyloid degeneration of the muscle fibers of the media. Arndt describes aneurysms as due to disease of the vessel wall *sui generis*. The muscularis relaxes, later becomes amyloid or entirely disappears, and the intima and adventitia form the wall of the aneurysm. He found no evidence of atheroma in the smaller arteries of the brain.

Eichler describes four cases, two with hemorrhage, in which he found miliary aneurysms. He believes they are true aneurysms

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and owe their origin to chronic endarteritis, which is identical with arteriosclerosis. According to him, dissecting aneurysms are to be sharply separated from miliary aneurysms. The former are simple hematomas of the vessel wall, and are never the cause but are the result of hemorrhage. Turner in 1882 described three cases, in only one of which were numerous miliary aneurysms. He speaks of thickening of the adventitia, diminution or disappearance of muscle nuclei of the media, and increase of nuclei and swelling of the intima. Hence, as a name for the condition, he regarded arteritis as being more appropriate than periarteritis. He also believed it probable that hemorrhage does not occur from rupture of miliary aneurysms, but from vessels with inflamed, softened walls.

Marchand stated that miliary aneurysms are undoubtedly due to changes in the intima." Birch-Hirschfeld states that the genesis of miliary aneurysms is not other than that of aneurysms in large vessels in which disease of the muscularis is the chief lesion. Kromayer found miliary aneurysms in a case of progressive paralysis of the insane. He describes periarteritis and colloid degeneration of the media which extends from without inward; these processes lead to aneurysm formation. According to this observer, arteriosclerosis of small cerebral arteries cannot lead to aneurysm formation.

Löwenfeld studied seventeen brains from cases of apoplexy; in all were miliary aneurysms. In some instances he found all three vessel coats intact over the aneurysm. He does not believe these formations are due to changes in the intima, but also objects to the theory that makes the muscularis exclusively responsible for them. He cannot support Charcot and Bouchard in the statement that hemorrhage comes in all instances from miliary aneurysms, as in two cases he found hemorrhage from diseased vessels showing no aneurysmal change. As Löwenfeld's microscopic studies were essentially all upon isolated vessels, stained or unstained, that were not sectioned, his work, so far as the microscopic findings are concerned, must be rated in value with that of Charcot's.

In 1887 Eppinger published an exhaustive contribution to the study of aneurysms. He divides aneurysms in general into congenital, parasitic, and simple traumatic. He says the so-called aneurysms found in the brains from cases of cerebral hemorrhage cannot be grouped with any of these forms, and hence are not aneu-

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rysms. They are (1) more or less circumscribed collections of blood in the lymph space between the media and adventitia—so-called aneurysma dissecans; (2) solid swelling of sections of the perivascular lymph space produced by the presence of various materials, as blood, lymphoid cells, fat, and pigment. Chronic periarteritis, as a result of the irritation thus induced, is common; in this connection the periarteritis of Charcot and Bouchard comes into consideration, but only as an accompanying phenomenon of a change that is not aneurysmal; (3) the perivascular lymph space can also appear as a mucoid-like solid mass, homogeneous or with striæ running chiefly at right angles to the vessel lumen.

Mendel by means of apparatus demonstrated that the blood pressure in the arteries of the basal ganglia is greater than in the other parts of the brain. These arteries consequently become increased in diameter and their walls stretch in the long axis. Frequent repetition of this leads gradually in advancing age to atrophy of the muscularis and then to miliary aneurysms. A new increase of blood pressure causes rupture of these aneurysms and hemorrhage. Ziegler states that cerebral hemorrhage comes from the bursting of arteries when the walls have been weakened by degeneration and inflammatory changes; aneurysmal dilatation of the vessels may occur before rupture.

Kaufmann asserts that in persons beyond middle age one frequently finds changes in the arteries of the brain, the larger being sclerotic or atheromatous, the smaller in part showing hyaline or fatty degeneration or calcification. The smallest and slightly larger arteries often bear miliary aneurysms. Elsewhere he describes these aneurysms as spindle, globular, or saccular formations in which all the layers of the vessel wall take part. In most cases the wall is simply thinned, or the muscle elements may at the same time be fatty or granular; the muscularis may not be visible. A rapid lessening of resistance and stretching of the media is the essential feature. In other cases the wall of the sac is thicker, the neck only being thinned; at the latter place entire separation may occur

Monakow describes the formation of miliary aneurysms as due to the media becoming atrophic or granular, thus causing the wall to become less resistant and allowing it to dilate. The intima becomes concerned, either in extensive or limited degree, in the

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regressive process. Finally, all three layers fuse into a membrane which constantly becomes thinner, is displaced outward, and finally appears covered only by the here and there thickened adventitia. The fact that the intima is very frequently involved in the changes shows that the pathological process leading to aneurysm formation, even if it be a peculiar process, is still related to arteriosclerosis; an endarteritic lesion, however, is not necessary for the formation of miliary aneurysms.

Osler says the weight of opinion now is that the media first degenerates. He also states that "endarteritis or periarteritis in the cerebral vessels most commonly leads to apoplexy by the production of aneurysms, either miliary or coarse. There are instances in which the most careful search fails to reveal anything but diffuse degeneration of the cerebral vessels, particularly of the smaller branches; so that we must conclude that spontaneous rupture may occur without the previous formation of aneurysm." Finally, Osler observes that the origin of the miliary aneurysms is disputed.

These statements of Osler well illustrate the lack of definite knowledge and consequently the conflicting opinions regarding the arterial changes and the aneurysms found in cases of cerebral hemorrhage. This obscurity, as I have already emphasized, is largely due to the inadequate methods formerly employed in the microscopic study of these brains. Surely the condition of the various coats of an artery cannot be accurately determined by mounting the entire vessel and examining the inner as they lie beneath the outer layers, the technique employed in many of the reported studies. I have found no report, in recent years and based on modern technique, of a series of cases sufficiently large to furnish reliable data concerning the question at issue. As such data appeared highly desirable, the present study was undertaken. For the material investigated and for confirmation of my work I am indebted to Professor Ludwig Pick, Prosector of the Friedrichshain Hospital, Berlin. To him I hereby extend my sincere thanks for his many courtesies.

2. MATERIAL STUDIED. The material on which this paper is based consisted of thirty-one brains from cases of spontaneous cerebral hemorrhage. As may be seen from the accompanying table, thirteen of the subjects were men and eighteen were women. This proportion of 58 per cent. of women to 42 per cent. of men is unusual

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for a series of cases. Monakow quotes Gintrac as finding in his collection of 706 cases, 57.6 per cent. men, and 42.4 per cent. women; Falret's 2297 cases included 72.2 per cent. men, 27.8 per cent. women; Kelynack and Bythell's percentages were 77 of men and 23 of women. The proper interpretation of my figures, I believe, is to regard them as a further instance of how a small series of cases may, in the absence of extensive statistics for comparison, be misleading.

The age of twelve of the men and of fourteen of the women in my series was known. That of the former group varied from forty to seventy-seven, that of the latter from thirty-four to eighty-two years, the average of the men being 60.5; of the women, 59.5 years. By decades the ages were:

30 to 40	1—woman.
40 to 50	3—men.
50 to 60	7—1 man and 6 women.
60 to 70	9—5 men and 4 women.
70 to 80	5—3 men and 2 women.
80 to 90	1—woman.

The four women and one man whose ages were not obtainable were apparently between sixty and seventy years.

Hemorrhage occurred in the left side of the brain in sixteen cases, in the right in twelve, in both sides in one, in the pons in one; in one there was no visible source of the blood which was in all the ventricles.

3. Gross Appearance of the Brains. As in all reported series of cases, the great basal ganglia were the parts of the brain most frequently involved. The corpus striatum was partly or entirely destroyed in twenty instances; the thalamus in nineteen; a cerebral peduncle in three, the pons in one, an occipital lobe in two, a parietal lobe in two, and the cerebellum in one. The degree of tissue destruction ranged from a circumscribed area one or two centimeters in diameter to the almost entire disintegration of the basal ganglia of a hemisphere. In twenty-seven of the thirty-one cases the hemorrhage had ruptured into a lateral ventricle and one or several of the ventricles were filled with fluid or partly clotted blood.

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TABLE OF THIRTY-ONE CASES OF CEREBRAL HEMORRHAGE.

No.	Sex.	Age.	Location of hemorrhage.	Vessels of base.	Heart.	Kidneys.
1	M	77	R. Internal capsule and lenticular nucleus	Moderate atheroma	Hypertrophy, left ventricle	Interstitial nephritis
2	M	62	L. Internal capsule and thalamus	Advanced atheroma	Hypertrophy, both ventricles	Interstitial nephritis
3	M	48	R. Corpus striatum	Moderate atheroma	Hypertrophy, left ventricle	Parenchymatous nephritis
4	F	58	R. Corpus striatum	Advanced atheroma	Hypertrophy, left ventricle	Diffuse nephritis
5	F	82	R. Corpus striatum, thalamus, and pons	Advanced atheroma	Hypertrophy, both ventricles	Diffuse nephritis
6	F	51	L. Occipital lobe	Moderate atheroma	Hypertrophy, both ventricles	Parenchymatous nephritis
7	M	70	L. Corpus striatum and thalamus	Moderate atheroma	Hypertrophy, left ventricle	Parenchymatous nephritis
8	M	40	L. Thalamus R. Thalamus and lentic. nucleus	Slight atheroma	Hypertrophy, left ventricle	Chr. parenchymatous neph.
9	F	50	R. Parietal lobe and post-central gyrus	Slight atheroma	Hypertrophy, left ventricle	Diffuse nephritis
10	F	65?	L. Thalamus and lentic. nucleus	Slight atheroma	Hypertrophy, left ventricle	Slight interstitial nephritis
11	M	58	R. Thalamus and peduncle	Advanced atheroma	Hypertrophy, left ventricle	Parenchymatons nephritis
12	F	50	L. Occip. lobe, peduncle, and thalamus	Advanced atheroma	No hypertrophy	Diffuse nephritis
13	F	52	L. Thalamus and lentic. nucleus	Advanced atheroma	Hypertrophy, both ventricles	Parenchymatous nephritis
14	F	34	L. Thalamus, peduncle, and lentic. nucleus	Extreme atheroma	Hypertrophy, both ventricles	Parenchymatous nephritis
15	F	70	L. Thalamus and corpus striatum	Advanced atheroma	Hypertrophy, left ventricle	Parenchymatous nephritis
16	F	65?	L. Entire basal ganglia	Advanced atheroma	Hypertrophy, both ventricles	Interstitial nephritis
17	M	46	R. Corpus striatum	No atheroma	Hypertrophy, left ventricle	Interstitial nephritis
18	F	55?	L. Thalamus	Moderate atheroma	Hypertrophy, left ventricle	Interstitial nephritis
19	M	73	R. Entire basal ganglia	Advanced atheroma	Hypertrophy, left ventricle	Interstitial nephritis
20	M	60	L. Entire basal ganglia	Moderate atheroma	Hypertrophy, left ventricle	Parenchymatous nephritis
21	F	53	— No evident source	No atheroma	No hypertrophy	Normal
22	M	60	L. Thal. intern. caps. and lent. nucleus	Slight atheroma	Hypertrophy, left ventricle	Arteriosclerotic
23	F	60?	R. Cerebellum	Advanced atheroma	No hypertrophy	Parenchymatous nephritis
24	F	68	R. Thalamus and corpus striatum	Moderate atheroma	Hypertrophy, left ventricle	Parenchymatous nephritis
25	M	70?	— Centre of pons	Advanced atheroma	Hypertrophy, left ventricle	Interstitial nephritis
26	M	65	R. Thalamus and posterior part of caudate nucleus	Advanced atheroma	Hypertrophy, left ventricle	Diffuse nephritis
27	M	67	L. Corpus striatum	Moderate atheroma	Hypertrophy, left ventricle	Diffuse nephritis
28	F	69	L. Corpus striatum	Moderate atheroma	Hypertrophy, left ventricle	Interstitial nephritis
29	F	61	L. Thalamus	Advanced atheroma	Hypertrophy, left ventricle	Interstitial nephritis
30	F	71	L. Thalamus	Slight atheroma	No hypertrophy	Parenchymatous nephritis
31	F	65	R. Corpus striatum	Moderate atheroma		

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The walls of the hemorrhagic foci were formed by irregular surfaces of brain tissue, extensively torn and jagged in some instances, in which were embedded masses of blood; at many points were exposed vessels. On the latter, or on those made visible later by maceration, were found in twenty cases macroscopic aneurysms. These formations varied in number from two to twenty in each specimen, a large majority of the brains showing less than ten, and many less than five, each. They were globular or fusiform masses from 0.5 to 4 mm. in diameter. A few were saccular formations projecting from the side of a vessel but the great majority were uniform swellings, with the vessel as the central axis; occasionally one appeared as a terminal bulbous enlargement. They were, without exception, dark red in color and of firm consistence.

In addition to these unruptured aneurysms there were found in four brains ruptured sacs varying from 1.5 to 8 mm. in diameter. Two of the five specimens observed (one brain contained two) were in the form of relatively small openings in the periphery of an aneurysm; the remaining three, which were larger, were only segments of empty shells, the remainder of the sac evidently having been carried away during the disruption of the tissues. In one case such a fragment of sac was visible in the fresh specimen, and later a second ruptured aneurysm was found in a macerated portion of the same brain. Vessels leading to these ruptured sacs were demonstrable in only two instances.

4. General Microscopic Appearances of the Tissues Studied. A routine microscopic study was made of twenty of the thirty-one brains. The organs were first examined in the fresh state to determine the presence or absence of microscopic vessel changes, especially of aneurysm formation. Numerous small pieces of the lacerated, pulpy portion bordering the hemorrhage were then removed and macerated in water to permit further search for aneurysms. The remainder of the brain was placed for two or three days in 10 per cent. formalin for preliminary hardening and then cut into thin slabs by numerous transverse vertical incisions. From these slabs of each brain were then taken from different points, bordering or at some distance from the hemorrhagic focus, six to ten blocks of tissue, which, after further fixation, hardening, and clearing, were embedded,

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the larger in celloidin, the smaller in paraffin. The remaining eleven brains, after isolated aneurysms from three of them had been removed for sectioning, were macerated and examined only as gross specimens.

Owing to the great amount of material collected, serial sections, except of isolated aneurysmal vessels or of occasional blocks, were not attempted. The celloidin blocks, however, which included more than two-thirds of the material, were entirely sectioned; the sections not at once mounted in the usual way were examined after they had been stained by hematoxylin, and in this way many more were selected for permanent mounting. The routine stains employed were hematoxylin, with the addition of eosin or Van Gieson, and Weigert's stain for elastic tissue. In addition, sections were stained by orcein, carmine, Weigert's stain for fibrin, osmic acid, and by methyl violet for the detection of amyloid.

As regards their general microscopic appearances, different brains in the series show differences in degree rather than in kind. In sections from all are few or many areas of hemorrhage varying from fifty or one hundred microns to several millimeters, occasionally over a centimeter, in diameter. In one extreme case entire sections are composed largely of medium-sized areas of hemorrhage that are at many points almost confluent. Most of these blood collections are in some portion of their extent in demonstrable relation to vessels, small or large. In the majority of instances the blood surrounds the vessel in an eccentric zone. In most of the smaller areas the blood is within the perivascular lymph space only; in some of these, and in all of the larger, it has also invaded the cerebral tissue.

In a few cases the results of old hemorrhages are present. These include simple pigmented areas, more or less circular scars, with at least the periphery pigmented, and finally what were probably aneurysms, with thick, badly stained walls and little or no remaining lumina. Around many of the moderately recent hemorrhagic areas are numerous phagocytic cells containing pigment granules and red blood cells, the "contractile" cells of von Recklinghausen. At points the neighboring ganglion cells contain many pigment granules. The borders of the gross hemorrhagic areas are roughened by projecting masses of normal or degenerated brain tissue and adherent blood;

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in many places are transverse or oblique sections of bloodvessels that are embedded in the wall or project to varying distances beyond.

5. MICROSCOPIC CHANGES IN THE INTRACEREBRAL VESSELS. The microscopic findings in the intracerebral bloodvessels, though exhibiting differences, are essentially the same in all the brains, or can be easily grouped. To avoid the frequent repetition that would occur if they were taken case by case, I shall give a summary of the lesions by describing (*a*) the intima; (*b*) the media; (*c*) the adventitia; (*d*) aneurysms; (*e*) the formation of aneurysms; (*f*) the actual source of hemorrhage.

(*a*) *Changes in the Intima.* The description here given applies particularly to the smaller arteries, though some of the medium-sized and larger show pronounced changes. The endothelial cells at points show proliferation. This in some vessels has resulted in new tissue formation, producing a high grade obliterative endarteritis, though the pure type of this lesion, without regressive changes in the new tissue, is not of great frequency. Glandular and vacuolar degeneration of the endothelium is also present in some vessels, and in many there are extensive areas where the layer is almost entirely lacking; some of the cells are strewn about in the blood content of the vessel, others, judging from the condition of those still present, having entirely disintegrated. At points the endothelial tube is slightly raised from the connective tissue beneath, and a few red cells or leukocytes are between them. In other vessels the endothelium is fairly well preserved, even in cases where it, with the remainder of the intima, is involved in pronounced general changes.

In many specimens the intima, including the elastica interna, shows extensive thickening and degeneration. For example, in sections from Case 4, an artery of 0.1 mm. outside diameter is seen for some distance in longitudinal section. At various points, in some for considerable length, the elastica is split into two or three principal and several thinner layers with degenerated cells or granular debris between. At one point the two outer layers are twenty-six microns apart, in the included space being a few cell nuclei surrounded by a mass of vacuole-containing granular debris, in which protoplasmic outlines are nowhere discernible. The narrower bands of the elastic tissue also show disintegrative changes.

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Splitting of the elastica interna into several or many layers, with more or less extensive fragmentation accompanying it, is a prominent feature of the intimal changes in all the brains studied. In sections from Case 2 the elastica of a vessel, which here has a lumen of 0.09 mm., in cross-section, shows separation at points into four, for the most part into three, layers. The innermost layer holds essentially the same relation to the vessel lumen as in normal vessels, while for four-fifths the circumference the two outer layers form a somewhat frayed and less deeply stained band which is at the widest point 0.15 mm. from the inner layer. The space between these widely separated layers of elastica is for the most part occupied by a granular, mesh-like material, poorly stained, in which are many small, almost circular spaces presenting the appearance of fat droplets. A narrow rim of tissue not entirely degenerated is on the outer border of the inner layer, separating it from the granular material described. In this substance, and also between some of the layers of the elastica where four are present, are numerous granules or small masses of brownish pigment. This splitting and degeneration of the elastica causes to some extent distention of the vessel, but is largely at the expense of the lumen, which is shown in other sections to be 0.24 mm. in diameter. In another section from this same case a vessel of 0.09 mm. lumen, in longitudinal section, shows splitting of the elastica for some distance, with an almost clear space between the parts and with pronounced bulging outward of the outer layer.

Sections from Case 10 show a vessel of 0.2 mm. lumen in which for half the circumference the intima is greatly thickened by new cellular tissue, which at one point is ninety microns thick. The nuclei in this tissue are quite well stained, but the protoplasm and intercellular material are partially granular and show indifferent microchemical reactions. Stained for elastic tissue, this area shows the elastica split into three or four moderately distinct and numerous other thinner fragmentary layers, which extend irregularly through the outer portion of the new tissue. At one point, where this splitting and fragmentation is most pronounced, there is only a broad mass of irregular, thin, poorly stained fibers instead of a thick, dense band, as on the opposite side of the vessel. Between some of the fibers

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are fairly large spaces, almost empty or partly filled by granular material of indefinite staining properties.

Of special value as bearing upon (1) priority in involvement of the coats of these vessels, and (2) the pathogenesis of aneurysms, is an intimal lesion found in many of these brains. This lesion is rupture of the intima with consequent passing of blood beneath that structure and dissecting for a variable distance between the elastica interna and the media. In some of these vessels the intima shows distinct degenerative changes in the endothelium and connective tissue, with at times disappearance of the former or a blending of both layers into a granular mass the components of which cannot be differentiated. The elastica also shows regressive changes at the point of separation, though splitting of that layer is not a feature of these specimens.

This lesion of the intima is well shown in sections from Case 7. In a vessel of 0.18 mm. lumen, cut diagonally, the intima for a distance of 0.28 mm. is separated from the media and the intervening space is almost entirely filled by blood. At the widest point the intima is elevated from the media a distance of seventy-eight microns, extending into the lumen of the vessel almost half the width of the latter. This specimen does not show the point of rupture of the intima, but for some distance this layer is a swollen, granular, or almost homogeneous material in which throughout its entire width are scattered or thickly placed red cells. The endothelium is absent from almost the entire vessel wall, some of the cells being free in the lumen among the erythrocytes. The elastica at other points is swollen, granular, or hyaline in appearance, and occasionally slightly separated from the media; no blood cells are in these small spaces; the media under the dissected intima is, with the exception of one or two points, intact. At one place are degenerative changes with vacuole formation; here a few red cells are within the limits of the media. Another section shows for a short distance about the middle of the involved area distinct granular degeneration and slight necrosis of the media; this extends through one-third the thickness of this coat, the remainder of which, with the adventitia, is slightly projected outward.

Sections from Case 18 show very strikingly a ruptured intima

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with blood dissecting between that layer and the media. In a vessel of 0.15 mm. lumen in longitudinal section, the intima on both sides for a distance of 0.45 mm. is dissected loose from the media; the layers from the two sides where they are the farthest from the media approach to within forty microns of each other, thus narrowing the lumen of the vessel to that diameter. At this point both the intimal layers are almost entirely lacking for a distance of forty microns, the gap being occupied by red cells which, on the one hand, are directly continuous with those in the vessel lumen, and on the other, with those beneath the intima. The endothelium is partially absent; the remaining cells are swollen, granular, and contain pigment. In a few places elsewhere than the dissected area the endothelium and connective tissue of the intima are raised from the elastica for a short distance, and leukocytes are in the spaces thus formed.

Nearly opposite the gap in the intima on one side of the vesse the media shows a small area of degeneration that extends almost to the adventitia. This is only a few microns long, and the remainder of the media and the adventitia show no bulging. Outside of this for some distance, especially on one side, the adventitia is split into three layers, and in the two spaces thus formed are red blood cells, the outer collection forming quite a thick mass that extends for some distance in the long axis of the vessel. On the opposite side of the artery the adventitia is also split and has blood in the spaces. The whole vessel is entirely surrounded by a mass of blood, the width of which on one side is three times the diameter of the artery itself.

To summarize: The striking changes in the intima of the arteries in this series of brains are two: (1) The lesions of arteriosclerosis, or "atherosclerosis" of Marchand. This is so constant in the specimens studied and is so often unaccompanied by, or is more pronounced than, changes in the media, that it must be regarded as the primary lesion in these diseased vessels. In addition, it may be said that the condition of the elastica as here described points quite clearly to that structure being primarily at fault, and hence lends support to the view taken by Coplin, as based on a study of arteriosclerotic vessels in various tissues other than the brain. (2) Rupture of the damaged intima, with consequent dissection of that coat from the

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media by blood which has passed between the two layers. This lesion is demonstrable in several of the brains in this series, and is, to the best of my knowledge, here described for the first time in connection with the pathology of cerebral hemorrhage. According to Monakow, it had not been found previous to 1905, and I have seen no reference to such observation since his statement was made. The significance of this process will be discussed later in connection with the question of aneurysm formation.

(*b*) *Changes in the Media.* With the possible exception of one case, the media of the vessels in this series of brains shows no changes that can be regarded as primary, or, in other words, independent of the intimal lesions already described. Lesions of the media are present in many instances in conjunction with the intimal degeneration, but only apparently as secondary or at least accompanying features. The possible exception to this general rule is found in the vessels of certain blocks of tissue in Case 7. Here the media shows granular degeneration and in many places deposits of lime salts. In some instances the entire media is thus converted into a tube of granular and calcareous material extending for some distance in the length of the vessel; in others the degeneration and calcareous deposit are only in patches, involving here a part or the entire thickness of the media. Even in these vessels the intima is in many instances considerably thickened and the elastica is split, at points into as many as five layers. For the most part the elastica shows relatively slight regressive changes as compared with many of the sections described, but at points it is made up only of a mass of indistinct fibrillæ which stain less sharply than does normal elastic tissue. In this case it is difficult to say that the medial change was primary, but the general impression given by the sections is that such may have been the case. In sections from other blocks from the same brain, however, intimal changes are the prominent feature.

In many vessels in which changes of the intima have been described, the media also shows changes, some of them pronounced. These include granular and fatty degeneration, and actual necrosis or disappearance of parts. In some instances blood has extended into this layer through the damaged intima, in a few vessels entirely through the media. The description of such vessels will be taken

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up later when discussing the pathogenesis of aneurysms. Suffice it to say here that in none of the intracerebral vessels of the brains studied has there been found primary atrophy, colloid or hyaline degeneration, amyloid transformation, or other special change of the media upon which stress has been laid by a number of previous writers upon this subject.

(*c*) *Changes in the Adventitia.* These brains contain no vessel from which can be concluded that a change in the adventitia is in any way causally implicated in the degenerative changes of the intima and media already described. The periarteritis pictured by Charcot and Bouchard is conspicuous only by its entire absence. Collections of cells are at times found around aneurysms or ruptured vessels, but otherwise not, even in the numerous instances of extensive intimal changes already described. The changes observed consist in separation of the adventitia from the media by blood, splitting of the adventitia into two or more layers with blood between those layers, and rupture of the adventitia along with the other coats as a part of the phenomena in the formation of false aneurysms. The chief point to be emphasized here is the absence of changes that can be considered primary in this coat of the vessels; periarteritis as a lesion leading to cerebral hemorrhage in this series of cases is therefore absolutely to be excluded.

(*d*) *Aneurysms.* In preparations from sixteen of the twenty brains of which portions were studied microscopically, there are found in connection with vessels or in cross-section without visible attachment, formations varying from 0.04 to 2.4 mm. in diameter. These structures are well represented by a specimen from Case 1 in which such a body 0.7 mm. in diameter is attached to a vessel of 0.05 mm. lumen. The inner coats of the vessel wall at some distance from the aneurysm show no prominent change, except at one point the intima is thickened and is partially degenerated. Other sections on which the aneurysm is not so centrally placed show such points with a mass of leukocytes and a few red cells beneath and among the endothelium and extending through the connective tissue to the elastic lamina. The adventitia is split into two layers on each side of the vessel, the two being separated to some distance by means of blood; this dissection of the adventitia extends to a much greater

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distance on one side of the vessel than on the other, and becomes more marked the nearer the aneurysm is approached. Near the aneurysm, one side of the vessel wall shows pronounced regressive changes. The intima is no longer recognizable, and the media is a granular structure, with nuclei only partially visible.

With these changes the vessel continues until at a certain point the wall, after it abruptly bends outward for a few millimeters on one side, on the other at once almost completely, loses its identity and the vessel is substituted by the globular structure shown in the wall. The adventitia continues for a very short distance over this mass as a recognizable band, but even here does not stain deeply. The wall of the aneurysm is made up of bands or fibrillæ staining yellowish or brownish yellow, and everywhere separated and infiltrated by red cells and leukocytes. The whole mass is surrounded by a large area of hemorrhage, and at some points this is so closely continuous with the contents of the aneurysm through the wall that the latter is hardly visible as a boundary, though a distinct rupture is not discernible. The contents of the aneurysm are partly red cells, partly leukocytes; in addition are numerous areas, rather toward the boundary in location, that stain lightly and are granular in appearance, as though remnants of blood clot, vessel wall, or other material. No recognizable constituent of the vessel wall is present as a boundary of the entire aneurysm.

Similar formations are found in fifteen of the other brains studied, most of them cut at right angles to the vessel, so that the latter is not seen. They vary in number in different cases, some showing several in many of the sections from each block, others in sections from one or two blocks only. In a part of those that show attachment to vessels, the adventitia is continued for a short distance from the termination of the vessel proper around the aneurysm, but this is the extent of the demonstrable coats of the vessel. In none of them has elastica been found in the aneurysm wall. In those in which the vessel attachment is shown, as in a section from Case 3, the elastica continues only to the margin of the aneurysm and exhibits extensive splitting and fragmentation, as already described under the heading of changes in the intima. In this case are also sections of a globular aneurysm 1.8 mm. in diameter that was taken out of the

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hemorrhagic area and cut separately. It is filled with blood, and at some levels the cells in the central third or even half are agglutinated and at points show beginning necrosis. The thin wall, although enclosing the blood and retaining it when separated from the brain tissue, cannot be definitely labelled as to structure. No stain gives a picture characteristic of connective tissue, muscle, elastica, or fibrin. In the wall at points, and also extending for some distance into the aneurysm itself, are small collections of bacteria, chiefly diplococci.

The description of other similar aneurysms of various sizes might be almost indefinitely multiplied. It will be noted that in none of them, with the exception of the adventitia extending a short distance in some instances, has any of the coats of the bloodvessel been found to form a boundary; they are, therefore, according to the generally accepted classification, spurious or false aneurysms. Benda maintains that a separation between true and false aneurysms cannot be made, as the wall of an aneurysm consists in every case of a new formation essentially unlike the vessel wall and which comes either from that wall or from the surrounding tissues. He describes aneurysm as any pathological widening of the lumen of an artery due to changes in the wall and which at least partly is in connection with the blood stream. This simplifies the grouping of aneurysms, but as the distinction between true and false is generally employed, I have followed that grouping in this paper. In addition to those described, the nature of these aneurysms as found in the tissues studied are so well shown by several other specimens that their description is necessary to complete this topic.

In a section from Case 13 is a vessel of 0.03 mm. lumen shown for a considerable distance in longitudinal section. On one side is a saccular aneurysm, extending outward from the vessel for a distance of 0.165 mm. and parallel to the long axis of the vessel for 0.2 mm. The opening from the lumen of the vessel into the aneurysm, that is, the distance for which the vessel wall is lacking, has a width of twenty microns. The wall of the aneurysm varies from twenty to only one or two microns in thickness. On one side a thin layer of adventitia extends to a very short distance over the aneurysm, but with this exception the entire wall stains an indifferent

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brownish yellow or slightly reddish brown (Van Gieson), recognizable structures being absent. It is pigmented throughout. At one point, though not the thinnest, is a secondary bulging of the wall; here the material forming it is irregularly separated into layers, and between and largely throughout are red blood cells. The aneurysm, except for a small area of fibrinous material, which also occupies a portion of the outlet from the vessel, is filled by blood which stains fully as well as that within the vessel itself. The entire vessel and aneurysm are surrounded by a large mass of blood, which increases in size beyond the latter until it forms a large oval mass that in other sections appears to have bounded a second larger aneurysm. The endothelium of the vessel is present nearly to the border of the opening in the wall on one side; on the other it is not clear for some distance, the cells being swollen or detached and in the thickened part showing numerous quite large spaces which extend to the elastica. The media also shows here slight degenerative changes and pigmentation.

In another section from the same block this aneurysm was studied at another level; at the point of origin the intima of the vessel, inclusive of the elastic layer, is torn and one end is for some distance elevated; that is, extends into the lumen of the vessel as a valve-like flap. Beneath this, and extending entirely through an opening in the remainder of the wall, the blood in the vessel lumen is continuous with that in the aneurysm. The degenerated and pigmented media is present on each side of the opening for a little distance before the adventitia is met. In still another section the intima of this vessel, though the latter here bears no aneurysm, shows very extensive degeneration with splitting of the elastica as already described when considering the general intimal changes of the series.

Another very definite specimen of false aneurysm was found on a vessel of 0.2 mm. lumen taken from Case 22. The aneurysm was approximately 1.5 mm. in diameter in the fresh condition, and was situated on a vessel in the internal capsule as a symmetrical globular swelling. The vessel wall here shows marked changes, as will be noted in the further description of this case, consisting of new connective-tissue formation in the intima, with partial degeneration, splitting of the elastica, and the presence of blood and fibrin between

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the elastic layers and between the intima and media. In one of the sections from the aneurysm there is a clear opening eighteen microns wide through both the inner layer of new and degenerated tissue and the outer, the thinned media; the adventitia is not here present, or at least is not recognizable. For part of the circumference of the vessel on one side of the opening, the inner zone of new tissue is separated from the outer layer of the elastica, which is closely adherent to the media, by a zone of degenerated tissue that is essentially only an open space. On the other side for some distance the entire structure of the wall is fused into a solid mass. Through the opening in the wall extends a band of fibrin, leukocytes, and red cells which connects the partly fibrinous content of the vessel with that of the attached structure, the latter being a false aneurysm 0.4 mm. in greatest extent. The wall of the aneurysm is formed of lamellated fibrin, in the meshes of which are leukocytes and a few red cells. The vessel and aneurysm are surrounded by a larger mass, 1.3 mm. in maximum diameter, of red cells and delicate fibrin network, this being bounded by a quite thick compressed band of the same material. This larger mass is clearly the body that was in the gross specimen regarded as an aneurysm.

In Case 3, specimens from one block show on the cross-section of a vessel of 0.05 mm. lumen a false aneurysm a trifle greater in diameter than is the vessel itself. On one side the adventitia possibly extends for a very short distance over the aneurysm, but its identity is questionable. The remainder of the wall, which is quite thick, is composed entirely of the rather dense, yellowish staining fibrinous or indefinite material that bounds these aneurysms in general. The opening connecting the vessel lumen with that of the aneurysm is entirely clear for a width of five microns; bordering it are red cells attached to the degenerated vessel wall. In both vessel and aneurysm are red cells and many leukocytes. The intima and media of the vessel are fused into an almost homogeneous layer; at one point near the aneurysm the adventitia is split and separated to form a wide, oval space containing partly degenerated red cells and leukocytes.

The presence of large numbers of false aneurysms in the sections of tissue studied led to the question as to whether they were structures

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similar to those isolated in the gross specimens. The latter were regarded as without doubt the miliary aneurysms so much discussed since the publication of Charcot and Bouchard. Were these true aneurysms, or were they the false type such as were found in the sections? The most reasonable supposition was that they were of the same nature as those found in the sections, since the blocks from which the latter were cut were of tissue continuous with the lacerated parts in which the gross aneurysms had been found. In order definitely to decide this point, I serially sectioned freshly isolated and immediately hardened aneurysms from Cases 3, 11, 12, 13, 22, 24, and 28. Some of these represented clusters of aneurysms, three to five in number; others were single globular or fusiform masses with the vessel bearing them visible for some distance at one or both poles. The findings, some of which have already been mentioned under preceding topics, were the most instructive in this study. *Not one of these structures proved to be a true aneurysm.* They were simply masses of blood, fluid or partly coagulated, enclosed by walls of indifferently staining material, possibly in some instances degenerated remains of the vessel wall, in many cases demonstrably fibrin.

One of these aneurysms with the vessel projecting from opposite poles was from Case 22. It was nearly two millimeters in diameter. The vessel on one side at some distance from the aneurysm was purposely doubled in embedding, so that a number of longitudinal sections were obtained in addition to the transverse ones through the remainder of the vessel and the aneurysm. Microscopically the vessel on one side of the aneurysm shows proliferative changes in the intima with new connective tissue formation and also degenerative changes much more marked at some points than at others. At certain places the degeneration is specially pronounced in the peripheral part, forming a distinct space between the inner portion and the outer layer of the split elastica. The latter is split into many layers, some of the finer of which are among the new connective tissue. Between the layers are scattered red blood cells. A small mass of fibrin and red cells surrounds the vessel at a short distance from the aneurysm. The media is here intact. As the aneurysm is approached the changes in the intima become more pronounced.

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At one place for nearly one-fourth the circumference the elastica has entirely disappeared and the media shows granular degeneration and fragmentation. Farther on the media is markedly thinned and at points shows bulging. In the spaces between the outer portions of the degenerated intima, and extending at one point into and almost or quite through the latter, is a mass of fibrin containing in its meshes a few red blood cells. Finally, there appears a direct opening through the entire wall, with the formation of a false aneurysm, as already described in the early part of this discussion.

The further changes in the vessel consist in a gradually increasing degeneration of the coats which collectively stain less intensely and merge with the wall of the aneurysm as a mass of indifferently staining material among, or by the side of, threads of fibrin. Finally, there is left only a small space to mark the site of the vessel, the aneurysm wall having also disappeared. Around this space are numerous phagocytic or "contractile" cells. In the sections showing progressively these changes, the mass of blood and fibrin surrounding both the vessel and the aneurysm increases in size; when the vessel and aneurysm have finally disappeared there is left only this mass, with its denser boundary, to represent the aneurysm (!) which was observed macroscopically. No distinct point of rupture in the false aneurysm has been found, though in many places the wall is infiltrated by leukocytes and red cells. As the opposite extremity of the mass of blood is approached, degenerated fragments of the vessel wall are again met. In an order the reverse of that described, the wall becomes more perfect until the vessel is again present, still showing, however, the intimal degeneration as before described; it is also surrounded by a narrow and decreasing sheath of fibrin and blood as observed at the opposite pole of the aneurysm.

This specimen, then, shows very clearly extensive intimal disease of an artery, with blood in and between the layers of the intima, then between it and the media, and finally extending through the latter, thus forming a false aneurysm when the adventitia disappeared, as shown in the figure. The body that had in the gross specimen appeared as a typical globular miliary aneurysm was therefore only the collection of blood and fibrin resulting from the rupture of the vessel, and bounded only by fibrin containing small fragments of

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brain tissue. A part of the phenomena of the rupture of the vessel was the formation of a false aneurysm.

Another very instructive specimen in the way of showing the nature of a supposedly miliary aneurysm was found in Case 28. The specimen was a globular enlargement of a vessel with a slight continuation from one pole, though not extensive enough to make it a typical fusiform aneurysm. Sections cut as in the preceding specimen show a vessel of 0.15 mm. lumen, with pronounced intimal changes as before described. There is blood between the intimal layers and also at a few points extending through that structure, where it is most damaged, until the cells are in contact with the media; the latter, however, is not a prominent feature. The media also at points shows moderate regressive changes. The adventitia is not everywhere visible, but this is apparently due to a mechanical rather than degenerative cause. The vessel can be traced through every section mounted, and nowhere shows aneurysmal dilatation; rupture is not observed, though, from the appearance of the wall, extravasation might readily have occurred. As in the other instances, the globular mass simulating an aneurysm is a collection of blood surrounding the vessel and bordered by a very thin rim of fibrin, with, in many sections, a band of brain tissue enclosing the latter.

The source of hemorrhage here is, curiously enough, a false aneurysm on a smaller vessel, possibly a branch of the larger, though not so shown, at some distance from the latter and nearer the centre of the blood mass. This small vessel shows degenerative changes such as have been described in other cases, and finally is transformed into an aneurysm. That this gave rise to all the hemorrhage cannot be positively stated, though from the larger vessel certainly not more than slight extravasation had occurred. However this may be, here was what appeared to be a typical macroscopic aneurysm, attached to a vessel which microscopically is shown to be absolutely without dilatation or even detectable rupture.

In Case 24, in addition to partial destruction of the caudate nucleus and thalamus of the right side, there was a small hemorrhagic focus 1.5 cm. in maximum length near the central part of the pons. In this space was a small bloodvessel with one end free and bearing laterally a slightly oval aneurysm 3 mm. in extreme length, this

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corresponding to the long axis of the artery. In the outer portion of the sac was an opening nearly half its length, clearly the point of rupture. After a drawing had been made of the specimen, which resembled very much that pictured by Gull, it was embedded and sectioned serially with results essentially as in the others described. The vessel shows pronounced changes in the intima, consisting at various points of enormous swelling, with granular and vacuolar changes in the endothelium, formation of cellular tissue on the surface of the intima, duplication of the elastica, and regressive changes. The media is mainly intact. The vessel was sectioned in the longitudinal direction, and a clear point of rupture was not found, though the vessel ends abruptly at a damaged area corresponding to the situation of the aneurysm, and is similar here to those places in other vessels showing rupture. The supposed aneurysm, as in the other instances, is only a collection of blood in the cerebral tissue, with enough fibrin to increase slightly the consistency and resistance. Nowhere is there aneurysmal widening of the vessel. The specimen then is only a false aneurysm, the fragile boundary of which had given way at one point, and thus produced the larger hemorrhage.

In addition to the case just described, macroscopically ruptured aneurysms were found in three other brains, Nos. 4, 11, and 12, making four in all in which this feature was observed. In three of the cases the sac was not sectioned. As Case 24 included the vessel bearing the sac, it has been described in that group. In one of the aneurysms in Case 12 the sac, still attached to the vessel and showing a small rupture, has been preserved as a gross specimen. Another from the same case was sectioned.

These gross specimens appeared as segments of quite thin sacs partly embedded in the wall of the hemorrhagic areas and empty or containing a small quantity of adherent blood; the other parts of the sacs had evidently been entirely fragmented or else carried away in the debris and coagulum. In one the sac, broken at about the midpoint, was 0.6 cm. across. Microscopically these sacs show exactly the same as the smaller ones, namely, a boundary of fibrin and compressed or slightly involved brain tissue to which masses of partly clotted blood are adherent. Absolutely no recognizable structural elements are present. At one point in the wall of the

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largest is another aneurysm 0.1 mm. in diameter, more than one-half of which projects into the larger; the latter, by its encroachment upon the cerebral tissue as it enlarged, had partly surrounded and enclosed the smaller, thus furnishing unmistakable proof that the larger was not a true aneurysm.

These findings from (1) scores of aneurysms in sections of tissue; (2) the serial sectioning of aneurysms with the vessel at each pole; and (3) the microscopic study of macroscopic ruptured aneurysmal sacs, constitute in my opinion a complete demonstration of the type of these so-called miliary aneurysms. They are false aneurysms bounded by fibrin and involved portions of brain tissue or by fully degenerated and hence unrecognizable elements of the vessel walls.

(*e*) *Method of Formation of False Aneurysms.* The vascular lesions in these brains have been described with sufficient detail to show that the intima is the coat primarily and most extensively diseased. That this intimal lesion is responsible for the further changes, including the production of aneurysms, is not to be doubted, but the exact method of aneurysm formation is not so clear. The very nature of the aneurysms described makes it difficult to distinguish in all instances between aneurysm formation by the gradual yielding at one point of a wall first weakened by a diseased intima, and the same result produced by blood which at first worked its way between the layers of the wall—the so-called dissecting aneurysm. A majority of the writers upon this subject regard the dissecting aneurysm as bearing no relation to the miliary type. Eichler has already been quoted as saying that dissecting aneurysms are to be sharply separated from the miliary. The former, he says, are simple hematomas of the vessel wall; they are never the cause, but are the result, of hemorrhage. Monakow states that aneurysma dissecans are formations *sui generis*, which have nothing to do with miliary aneurysms.

These statements are evidently based on the supposition that the miliary aneurysms are true aneurysms in the sense of being dilatations of vessels still bounded by one or more coats of the vessel, without any two of them having previously been separated by blood; in other words, lack of dissection. According to the usual classification, the miliary aneurysms in my specimens must be denominated

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false aneurysms. This separates them from the dissecting form, which has for its boundary one or more coats of the vessel; according to most writers, the boundary is the adventitia, since they speak of dissecting aneurysms as collections of blood in the space between that coat and the media. This difference between the dissecting aneurysm and the fully formed miliary aneurysm, as I have found the latter, may therefore be conceded; that they are in every case distinct in the sense of not being stages in the same process, I am not ready to believe. On the contrary, the findings in some of my cases indicate very clearly that the false aneurysms there present, and which in the gross specimens appeared as the miliary type, began as the dissecting variety.

Dissection of blood between the intima and media, without further prominent change in the vessel wall, has already been described in two cases under the head of changes in the intima. Of great significance in this connection is the aneurysm described under Case 13. The fact that the vessel itself exhibits absolutely no dilatation, the intima continuing in a straight line except where a flap starting from the degenerated and ruptured point is raised to form an opening through which the blood has passed, shows very definitely that this aneurysm began as the dissecting type. As the aneurysm itself is a typical false aneurysm, the relation of the dissecting form to the latter is thus well shown, although, of course, the stage with a collection of blood immediately beneath the adventitia cannot be demonstrated because that structure as such has disappeared.

That blood dissects through the media is shown by several of my cases. In Case 15 is an artery of 0.8 mm. lumen, the intima of which is a thickened, indifferently staining, pigmented layer possessing no elastica. The media stains by van Gieson a rather homogeneous yellowish brown, though in some parts the muscle fibers can easily be distinguished. At one point in the wall the thickened intima is separated into irregular layers, and between them is blood. Columns of red cells at points extend also into the media, in one instance occupying a space forty-six microns long where the media has practically disappeared, leaving only an exceedingly thin film of that layer between the blood and the adventitia. At another place in this wall there is an oval collection of blood 0.15 mm. in length between

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the media and adventitia. The latter coat is very slightly elevated, but the space for the blood is obtained largely at the expense of the media, which is greatly compressed under this area and with the intima is displaced inward, encroaching sufficiently upon the lumen to slightly more than overcome the concavity of the vessel wall.

Passage of blood through the intima and media is further shown in a vessel of 0.15 mm. lumen in Case 7. At one point there is a diagonal opening with a maximum width of eleven microns extending entirely through intima and media, this channel being densely packed with red cells that are in direct continuity with these in the lumen of the vessel. At this place in the wall, and for some distance on the side toward which the diagonal opening points, the adventitia is split into layers which are elevated to various distances, the spaces under and between them being occupied by blood. At various points these adventitial layers cannot be clearly traced through the entire mass of blood, which is thus apparently continuous with that outside the vessel. Bordering the opening through the wall, the intima and media show pronounced degenerative changes. There is a fairly large hemorrhage surrounding the vessel, which in other sections exhibits extensively damaged intima and media but no rupture. This vessel is an example, then, of rupture of the two inner coats, with splitting and wide distention of the adventitia and at least extravasation of blood through the latter coat into the surrounding tissue.

From Case 3 are sections of small masses of brain tissue, one of which contained a small macroscopic aneurysm. Sections through the midpoint of the aneurysm show it to possess a maximum diameter of 0.8 mm., with a fairly thick fibrillated wall. From one point in this wall and continuous with it springs a second wall that is entirely within the space enclosed by the larger and is only half its size. The small, almost circular space bounded by this inner wall contains blood, as does also the larger space enclosing it; the latter terminates on each side, where the two walls become continuous, as a sharp angle. That part of the inner wall directly opposite to its point of fusion with the outer is several times as thick as the two where they are joined; it is loosely formed, and the outermost fibrillæ are projected outward by blood that is beneath and scattered to a slight

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extent among the fibrillæ of the inner portion. The diameter of the inner enclosed space is 0.3 mm., that of the outer 0.68 mm. Sections properly stained show that the inner wall is composed almost wholly of fibrin; the outer is also largely fibrin, but it contains at points indistinct bands of other material, more solid, which, however, gives by no method a characteristic stain.

Other sections show the inner wall to be more dense and nearly the length of the outer, being only a short distance from the latter at the point opposite to that where the two become fused as one coat. As before, the most extended parts of the inner wall are frayed or at places actually broken. Still other sections where the aneurysm is smaller show only one wall, no boundary forming an inner space being present. There is no hemorrhage immediately surrounding the aneurysm, which is everywhere bounded by brain tissue; at points are a few leukocytes adherent to or in the neighborhood of the wall. This specimen has been described with some detail because its general appearance is that of the remains of a vessel in which blood had distended various layers of the wall to different degrees, and thus formed a false aneurysm by the process of dissection.

That a part, possibly the greater part, of the false aneurysms found in these cases began therefore as the dissecting type appears to be fully established by these specimens. That some of the aneurysms arose from simple yielding of a diseased wall without dissection of the coats has also been clearly shown by preparations described under other headings. Hence the conclusion must be that the false or so-called miliary aneurysms may be produced by either of these two methods. To the dissecting aneurysm, therefore, must be attributed a much greater significance than it has hitherto received.

(*f*) *The Actual Source of Hemorrhage.* Monakow states that miliary aneurysms have been recognized by all later observers as an essential cause of bleeding, and serves today as the most certainly established source of cerebral hemorrhage. The disputed question now, he says, is whether they are the only cause; can vessel changes of other types, as atheroma, hyaline degeneration, etc., lead to bursting of vessel walls? This question, as propounded by Monakow, presupposes that the miliary aneurysms are special structures, and

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that one or more coats of the vessel still persist. In the light of my findings this question must be put in a different way, namely, is the bursting of these relatively slowly formed false aneurysms, or the blowing out, so to speak, of a segment of diseased but not aneurysmal vessel wall, without subsequent aneurysm formation, the source of hemorrhage? Or may both be responsible?

The findings in this series of brains indicate that both these methods are active in producing cerebral hemorrhage, the false aneurysms probably in the majority of instances. The presence in the gross specimen, in four of these cases, of ruptured aneurysmal sacs, with later microscopic study of three proving them to be false aneurysms, shows clearly that those structures rupture. In one, that of the small hemorrhage in the pons,the entire bleeding can unquestionably be attributed to this source. In some of the larger hemorrhagic areas, with their widespread destruction of tissues, the aneurysm there found may possibly have been torn by the disruption which followed hemorrhage elsewhere, though this can hardly be regarded as the most reasonable supposition.

In the sections of tissue a clearly defined rupture of the wall of one of these aneurysms has not been found, but in many of them the condition of the wall and of the surrounding tissues justifies the belief that they were the source of hemorrhage. In others, with thick fibrinous boundaries and the lumen itself largely filled by coagulum, it is very probable that hemorrhage would more readily occur from other parts of the diseased vessel wall than from the aneurysm itself. This, in fact, is shown in the case of one vessel, an unruptured false aneurysm of which has already been described. This vessel in another section, some distance from the aneurysm, shows almost entire disappearance of the intima, and for a long distance the media is degenerated. For one-third the circumference the adventitia is split and blood is between the layers. At a point on the opposite side of the vessel all three coats are lacking, and through an opening forty microns wide the content of the vessel is in direct continuity with the blood mass outside of and surrounding it. Here, then, is a clear instance of rupture of a diseased vessel without aneurysm formation. Furthermore, the same vessel bears at another point a false aneurysm, the diameter of the artery, that is

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unruptured; this is evidence that a diseased vessel wall can be less resistant to the pressure of the blood stream than is an aneurysm containing a coagulum.

In preparation from the same case is another vessel of 0.1 mm. lumen in diagonal section. The elastica is present, though split and fragmented, except for a short space. Here it is entirely lacking, one of the remaining ends being raised for a considerable distance by blood between it and the outer part of the wall. Near this the swollen and degenerated wall is dissected and split into layers, and through one of these long, narrow, diagonal passages there is a continuous chain of red cells from the lumen to a relatively small area of hemorrhage that surrounds the vessel. This artery not only shows hemorrhage without aneurysm formation, but also that it was brought about by a dissecting of the wall rather than by direct rupture. In Case 7 is a vessel of 0.03 mm. lumen in longitudinal section, in one side of which is an opening 0.05 mm. in length. Through this to a distance equal to the diameter of the vessel extends a mass of fibrin containing a few red cells. Around the outer portion is an indistinct boundary that possibly is adventitia, but which has lost distinguishing characters. The formation of the clot in this way appears to exclude the question of rupture of the vessel by tearing of the tissues during the larger fatal hemorrhage, although the vessel is in the border of that focus.

In various preparations are other small vessels showing ruptured walls. They are not described in this connection because of the possibility that the thin or diseased walls were torn by violence during the disruption of the surrounding tissues by the larger hemorrhage, which led to death of the subject. A sufficient number of undoubted instances has been given, however, to show conclusively that intracerebral vessels rupture without previous aneurysm formation. This is another point that this study, so far as I am aware, demonstrates for the first time, in stained sections of tissue, in this connection.

That the large hemorrhages, with their terrific destruction of tissue, so often found in cases of apoplexy, are as apt to occur from primary rupture of vessels as from the bursting of false aneurysms, I do not believe. In the latter condition a comparatively large area of vessel wall slowly, or possibly even quite rapidly, yields, but the

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blood is temporarily held in check by the surrounding tissue or by coagulation, or by both. When, however, the wall of the aneurysm finally gives way, the entire current of blood in the affected vessel may be thus instantly diverted into the tissues, with the widespread destruction so well known in these cases. I say the entire current of blood, because in many of my preparations the lumen of the vessel continues almost or entirely undiminished in caliber directly to the border of the aneurysm. That a sufficiently large segment of a small cerebral artery without aneurysm, no matter to what extent it may be diseased, gives way at any particular moment and permits a similar outflow of blood is hardly to be believed. That these explosive cases, to employ a term suggested by the condition of the cerebral tissues, are due to the rupture of aneurysms, even though none is visible in the resulting debris, appears therefore the most reasonable supposition. In other cases, also with large hemorrhages, but in which a single massive clot is found, a relatively slow leak through the ruptured wall of a vessel is more probable than is the bursting of an aneurysm. Laying aside, however, the question of massive hemorrhage, the fact that rupture of small arteriosclerotic intracerebral arteries takes place is of great interest in connection with the pathogenesis of small hemorrhages that give rise to paralyses and other non-fatal affections.

As this study was undertaken for the purpose of determining the pathology of the intracerebral vessels in cases of spontaneous cerebral hemorrhage, that aim has been strictly followed. Certain subsidiary points are usually considered in this connection, however, and these were noted in addition to the principal theme of the study. These points deal with the condition of the arteries at the base of the brain, the left heart, and the kidneys, and my findings are here briefly set forth as a supplement to what has already been described.

6. Condition of the Basal Vessels. The relation between lesions of the great vessels at the base of the brain and of the intracerebral arteries has given rise to much discussion. Löwenfeld states that an etiological relation of atheroma of the basal arteries to cerebral hemorrhage can be assumed in only a part of the cases. It appears that changes in the basal and in the intracerebral arteries develop usually, possibly always, independently of each other. Only

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in advanced endarteritis of the former, he believes, can the latter be directly affected, namely, by increase of blood pressure.

The condition of the basal vessels was noted by Charcot in sixty-nine cases as: very atheromatous, seventeen; moderately atheromatous, twelve; slightly atheromatous, twenty-five; unchanged, fifteen. He says there may be marked atheroma of the basal vessels and the branches to the meninges without the presence of miliary aneurysms in the brain, or there may be numerous miliary aneurysms with practically no lesion of the basal vessels; they may, however, and frequently do, coincide.

Weiss found, in thirteen cases of fatal hemorrhage, nine brains with extensive, four with moderate, arteriosclerosis of the basal vessels. Eulenberg found in his forty-two cases, twenty-nine with disease of the basal vessels. He concludes that the direct effect of chronic endarteritis of these vessels upon cerebral hemorrhage is very slight. Monakow supports Charcot as regards the lack of correspondence between the lesions of the two sets of vessels. Any relation between the two he considers as theoretical rather than based on facts.

With the intracerebral vessels in my series showing simply arteriosclerosis instead of a special pathological process peculiar to cerebral apoplexy, one might regard as probable a relation between its presence or severity in them and in the arteries of the base. It is true that if the latter vessels were arteriosclerotic, that lesion in their branches would not necessarily be an accompaniment or a result. Anatomically and physiologically, if we are correctly taught, there is reason for believing that this sequence would be more apt to occur in this location than elsewhere in the body. This reason is that the small vessels of the basal ganglia, notoriously the site of hemorrhage, are direct branches of the cerebral arteries, and hence are subjected to a blood pressure greater than vessels of similar size in other parts of the brain and possibly of the body. With this predisposition (if in our present haziness of knowledge upon the subject one dare employ this term) to arteriosclerotic changes inherent in these small vessels, an increased blood pressure in the basal arteries, due to sclerotic changes therein, might induce similar changes in their branches. Or, laying this question aside, if the basal arteries for whatever reason become arteriosclerotic, why are these direct, high-

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pressure intracerebral branches not apt simultaneously to become involved? In other words, the two not as cause and effect, but as the joint effect of a common cause. Theoretically, therefore, in arteriosclerosis, especially advanced, of the basal arteries, one should also find this process in their immediate branches within the brain.

In a general way, although there are exceptions, my cases support this postulate. In only two of the brains (Nos. 17 and 21) was atheroma of the basal vessels entirely lacking. The first was from a man aged forty-six years, the corpus striatum of the right side being the site of hemorrhage. The laceration of cerebral tissue was very slight as compared with most other specimens studied, there being little more damage than a cleft through the ganglion; this was bordered by, for these cases, unusually firm and smooth brain substance, in which only a few small hemorrhagic foci were visible. No macroscopic aneurysms were found in the fresh specimen or in the portions that were macerated. Microscopically the intracerebral vessels show no noteworthy lesions. In the border of the large area was found nothing to explain the occurrence of hemorrhage.

The second brain without basal atheroma was from a woman aged fifty-three years. In it was no visible laceration, and hence no evident source of the blood which was present in all the ventricles. No aneurysms were present. In the macerated specimen were no aneurysms or other lesions except in one artery, 0.2 mm. in diameter, which showed several tiny areas slightly yellow in color. This brain was not studied microscopically.

Of the four brains in which the basal vessels showed but slight atheroma, that is, a few small, widely separated patches, macroscopic aneurysms were found in but one. Two of the brains were thoroughly studied microscopically, and showed small aneurysms in the sections, but the arteriosclerosis was in general less marked than in most of the specimens with more extensive basal lesions. One of the three aneurysms found in the third brain of this list was sectioned, the artery bearing it showing pronounced arteriosclerosis.

In seven brains with moderate atheroma of the basal vessels, that is, numerous patches but none of great length and with moderate rigidity, and nine with advanced atheroma, that is, numerous confluent patches or long uniform areas and marked rigidity, no note-

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worthy differences in the microscopic lesions of the intracerebral vessels are present. One of the former list shows considerably less involvement than the others, but in general the two groups could in no wise be separated by the microscopic findings. Four in each of the groups were not studied microscopically.

The findings as regards macroscopic aneurysms when compared with the condition of the basal vessels are of interest. Macroscopic aneurysms were found in the cerebral tissues in eleven of the fourteen cases of advanced basal atheroma, in eight of the eleven cases of moderate atheroma, in one of the four cases of slight atheroma, and in neither of the two cases with no atheroma. Tabulated, the findings are:

ATHEROMA OF BASAL VESSELS.

Advanced,	14 cases.	Microscopic aneurysms in	11,	or 79	per cent.
Moderate,	11 cases.	Microscopic aneurysms in	8,	or 73	per cent.
Slight,	4 cases.	Microscopic aneurysms in	1,	or 25	per cent.
None,	2 cases.	Microscopic aneurysms in	0,	or 0	per cent.

Thus, so far as the presence of aneurysms is concerned, there was a constant rise in the percentage of positive cases as the basal atheroma increased in severity. The moderate and advanced groups differed the least, as they also do in the microscopic lesions. Aneurysms were absent, however, in cases, three of each, of both moderate and advanced atheroma of the basal vessels, thus supporting the statement of Charcot that they may not accompany such lesion. They were also found in one of the four cases of slight sclerosis.

Concerning the brains in this series of thirty-one cases, therefore, we can in general say, that in both its macroscopic and microscopic manifestations, arteriosclerosis of the intracerebral vessels was the more pronounced as atheroma of the basal vessels increased in severity. A point that should be investigated in this connection is the condition of the intracerebral arteries in brains showing various stages of basal atheroma, but in which hemorrhage has not occurred. The time at my disposal unfortunately did not permit the study of this phase of the subject.

Eichler describes two cases not dying from hemorrhage in which miliary aneurysms were found in the brain. The subjects were women, aged seventy-two and seventy-seven years respectively. As

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one brain showed encephalitic scars and the other foci of softening in the corpus striatum, there is the probability that small hemorrhages had in reality occurred.

7. CONDITION OF THE HEART. A second lesion of importance in connection with cases of cerebral hemorrhage is hypertrophy of the left ventricle of the heart. This affection is so intimately associated with those of nephritis and general arteriosclerosis that a discussion of any one of the three initiates what may with propriety be called a vicious circle in argumentative medicine. For this reason it will answer my purpose to consider briefly the opinions of some other writers, and then give my own findings.

Eulenberg states that hypertrophy of the left ventricle can favor hemorrhage only when it permanently raises the normal mean tension of the aortic system. This condition comes solely in cases of hypertrophy dependent upon peripheral circulatory changes, especially contracted kidney and diffuse arteriosclerosis, and never in hypertrophy due to valve lesion. In general, he continues, hypertrophy of the heart is an accompaniment of cerebral hemorrhage much less frequently than is arterial degeneration. He found hypertrophy of the left ventricle in six of the twenty-nine cases in which the basal vessels were diseased, and in three of the thirteen cases in which they were normal, a total of only nine, or 21 per cent., in forty-two cases.

Charcot found hypertrophy of the heart in twenty-two of fifty-five cases in which this point was noted, but in only 36 per cent. was this a simple hypertrophy, the only type that can be accused of increasing arterial tension. He therefore regarded this condition as only an accessory cause of cerebral hemorrhage. Weiss reports pure hypertrophy of the heart in twelve, or 40 per cent., of his thirty cases of hemorrhage.

Kaufmann states that as an essential influence in causing rupture of diseased vessels the chief factor is hypertrophy of the heart without dilatation, especially of the left ventricle, of the type that is found in contracted kidney. In addition to this are other chronic heart and arterial affections which cause an increase in blood pressure.

Monakow ventures no positive opinion upon the subject. He states it is not yet decided whether hypertrophy of the heart is a

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necessary mechanical consequence of renal disease or is caused by primary endarteritic disease of the entire arterial system and therefore also by the renal vessels. Until this question be decided, supposition that in contracted kidney the changes in the cerebral arteries are caused by hypertrophy of the heart lacks a sure foundation.

The condition of the heart was noted in thirty of my cases, seventeen women and thirteen men. Of the former, eight showed hypertrophy of the left ventricle, five of both ventricles, and in four the heart was normal. Of the thirteen men, the left ventricle alone was hypertrophied in twelve, both ventricles in one. Regarding the nature of this hypertrophy, I can say that in only six cases, all women, was there demonstrable valvular lesion. In each the mitral valve was affected. The lesions in the four with hypertrophy of the left ventricle alone were "chronic mitral endocarditis" in two, "mitral stenosis and insufficiency" in one, and "verrucose endocarditis of mitral and tricuspid" in one. In the remaining two of the six cases, with both ventricles hypertrophied, the lesion was classified as "mitral insufficiency." The percentage of cardiac hypertrophy uncomplicated by valvular lesion is therefore 41 per cent. in the women of this series, this corresponding quite closely to the figures quoted. In the male subjects the percentage of hypertrophy of the left ventricle, without valve lesion, is 100, an unusual finding.

Whether the hypertrophied heart plays a role in causing the arteriosclerosis leading to cerebral hemorrhage, or in the opposite manner its hypertrophy be induced by changes in the arterial system of which that of the brain forms a part, the actual effect of simple hypertrophy of the left ventricle upon diseased cerebral vessels can be only one, namely, to hasten their rupture. With the intracerebral vessels, from whatever cause, showing the lesions described in this paper, a rising blood pressure due to increasing hypertrophy of the heart is of greatest importance in precipitating fatal hemorrhage. More than this we are probably not in a position to say.

8. Condition of the Kidneys. As was mentioned when considering the heart, nephritis is one of a triad of conditions that cannot be weighed separately. If in a certain case contracted kidneys be the cause of cardiac hypertrophy, then, through the action of the

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latter upon the cerebral vessels, the nephritis may possibly play the initiative role in the production of cerebral hemorrhage. Löwenfeld states that contracted kidney must be given a place among the causes of this lesion, while Monakow regards it as certain that cerebral hemorrhage in nephritic subjects is due to no uniform cause.

I cannot see that my series of cases aids in clearing the obscurity surrounding this question. The thirty cases in which the condition of the kidney was noted are thus grouped: interstitial nephritis, ten; parenchymatous nephritis, twelve; diffuse ("parenchymatous and interstitial"), six; arteriosclerotic contracted kidneys, one; normal, one. These were diagnoses from the gross specimens, routine microscopic studies not being made. From this will be seen that though in only one case the kidneys were normal, the remainder showed no uniform lesion. Not only were the groups interstitial, parenchymatous, and diffuse demonstrable, but the individual cases showed various degrees of involvement ranging from slight acute parenchymatous nephritis to the typical contracted kidney. To relatively few of the interstitial group could be ascribed a primary part in the arteriosclerosis and cardiac hypertrophy, even if in general one were inclined to favor such view.

9. CONCLUSIONS. 1. The lesion of the intracerebral arteries in cases of spontaneous cerebral hemorrhage is primary in the intima, beginning apparently in the elastic layer, and is simply arteriosclerosis, or atherosclerosis, differing in no wise from that process as it is found elsewhere in the body.

2. In some cases this lesion progressively involves the media and adventitia, and leads at points to such weakening that simple rupture of the vessel wall takes place.

3. A circumscribed portion of the intima of an artery may give way and permit blood to pass between the coats of the vessel, forming the so-called dissecting aneurysm.

4. Both the simple rupture of the vessel wall and the dissecting aneurysm are followed by the formation of false aneurysms, though such formation does not occur in every instance.

5. The so-called miliary aneurysms of cerebral hemorrhage are false aneurysms, due primarily to arteriosclerosis, and are preceded

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by simple rupture or by dissecting aneurysm, probably more often the latter, of the affected artery.

6. Spontaneous cerebral hemorrhage occurs both from the rupture of false aneurysms and the rupture of vessels without previous aneurysm formation.

7. In general, but not invariably, the intracerebral arteriosclerosis corresponds in severity to that of the arteries at the base of the brain.

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November 12, 1908.

Exhibition of the Different Types of Cerebral Hemorrhage.

BY D. J. McCARTHY, M.D.

1. VENOUS HEMORRHAGE. In this case the patient suffered from advanced pulmonary tuberculosis. A hemorrhage 2 cm. in diameter is present immediately beneath the cortex, in the inferior parietal lobe of the left side. Microscopic examination shows this to have occurred some time preceding death. The small veins

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immediately surrounding the large hemorrhage are surrounded by masses of extravasated free blood cells undergoing degeneration without, however, any break in the walls of the veins. There was extensive thrombosis of the cortical veins.

This represents the type of venous hemorrhage secondary to thrombosis, produced by marked passive congestion.

2. EXTENSIVE VENOUS OSMOTIC HEMORRHAGE SECONDARY TO THROMBOSIS OF THE CEREBRAL SINUS. The hemorrhage in this case is microscopic. There was thrombosis of the lateral sinuses, straight sinuses, veins of Galen and cerebellar veins. Extensive areas in the brain tissue, *i. e.*, the optic thalamus, cerebellum, etc., presented a deep chocolate color as compared with the yellowish white color of the rest of the brain.

Microscopic Examination. This seemed to be due to an osmosis of the red blood corpuscles into the cerebral tissue, without gross destruction of nervous tissue or break in the vessel wall.

3. PRENATAL SUBARACHNOIDAL HEMORRHAGE OF THE BRAIN IN A STILLBORN CHILD. This case presents a marked atrophy of the right cerebral hemisphere, the posterior third of this hemisphere being entirely wanting. Its place was taken up by a subarachnoidal cyst filled with a bloody, grumous fluid. The meninges are stained a brownish black, which under microscopic examination is seen to be due to melanin.

4. EXTENSIVE HEMORRHAGE INTO THE PIARACHNOID. The entire prefrontal area of the left side is the seat of extensive extravasating hemorrhage. The source of the hemorrhage, *i. e.*, whether from the veins or arteries, cannot be determined from microscopic sections. There was extensive arteriosclerosis with some atrophy of the cortex. The patient from whom this brain was taken presented during her life time tabes dorsalis.

5. HEMORRHAGE INTO A CEREBELLAR CYST. The cerebellum in this case presents an extensive gliomatous process, the centre of which has degenerated into a cyst. Two days before death, the patient presented an epileptiform state. At autopsy the cyst was filled with a bloody, grumous fluid.

6. EXTRAVASATING HEMORRHAGE AT THE BASE OF THE BRAIN IN A CASE OF TUBERCULOUS MENINGITIS. This case presents

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extensive areas of hemorrhage of the pons, medulla and basal ganglia, complicating tuberculous plastic meningitis.

7. HEMORRHAGE OF THE CHOROID PLEXUS OF THE LATERAL VENTRICLES. This is from a case of fulminating tuberculous meningitis. In this case the choroid plexus of both lateral ventricles is distended with free blood, which fills up the interstices of the choroidal tissue.

8. HEMORRHAGE OF THE CEREBELLUM COMPLICATING PARESIS. This appears to be a localized hemorrhage in the right cerebral hemisphere, with extravasation in the cerebral meninges which is probably secondary to venous thrombosis in this area.

9. HEMORRHAGE OF THE PINEAL GLAND. Specimens from a case of advanced pulmonary tuberculosis showing hemorrhagic cyst of the pineal gland.

The above specimens present abnormal types of cerebral hemorrhage and the varying etiological factors which may induce the hemorrhagic state in nervous tissue. One group of these specimens is of value in showing the importance of an infectious process in the production of hemorrhagic cysts in the brain. The extensive hemorrhages seen in some cases of tuberculous meningitis indicates a tendency in certain bacterial infections to produce hemorrhage. In pulmonary conditions, the pneumococcus has been considered the most important bacteria in the production of hemorrhagic states. Whether the mixed pneumococcus infections are present in the above cases of tuberculosis was not determined.

DISCUSSION.

DR. W. G. SPILLER: Venous hemorrhage of the brain in my experience is far less common than arterial hemorrhage. Some eight or ten years ago I presented before this Society a specimen of thrombosis of the straight sinus with hemorrhage into the lateral ventricles. The superior longitudinal sinus had evidently been occluded a long time, as it was partially calcified. I have recently examined a case in which occlusion of the superior longitudinal sinus caused great distention of the veins upon the upper surfaces

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of the cerebral hemispheres, with profuse hemorrhage in the corresponding parts. The degree of hemorrhage that may occur in the brain is remarkable; in two instances I have seen a clot filling all the ventricles and making a cast of these cavities, with hemorrhage at the base of the brain, having its starting place in one cerebral hemisphere.

The hemorrhage into the cerebellar gliomatous cyst, shown by Dr. McCarthy, is interesting, and resembles the condition described by Gowers of spinal hemorrhage into syringomyelia. Uncomplicated cerebellar hemorrhage is very rare. Hemorrhage is not uncommon in or near brain tumor, and probably is caused by implication of the walls of bloodvessels in the tumor or by lessened resistance of the surrounding tissue. While the hemorrhage from sinus thrombosis may be in part from leaking, I believe it more commonly occurs from rupture of a vessel, even though the place of rupture may be difficult to find. Hemorrhage on the brain is probably more common than the text-books teach. It is not so likely to cause death as hemorrhage into the substance of the brain, and may as well as thrombosis be a cause of the yellow plaques found in the brain cortex at necropsies.

DR. JOSEPH MCFARLAND: In reference to the statement made by Dr. McCarthy that hemorrhages in the brain in some cases is due to the influence of microörganisms, is it not strange that we do not see the same in other organs of the body?

DR. MCCARTHY, closing: In answer to the President's question concerning the infectious cause of cerebral hemorrhage, I would state that I had something different in mind than Hektoen's type of intimal tuberculosis. I think that in a group of cases in both venous and cerebral hemorrhage the rupture is determined by a microörganismal cause. In venous thrombosis, as is well known, a bacterial factor is important in the production of the thrombus. Certainly the hemorrhages of so-called hemorrhagic encephalitis in the brain, are due to a bacterial agent. I have reason to believe that in some cases gross cerebral hemorrhage, secondary to rupture of a vessel, might be caused by pneumococcic and other bacteria as terminal or pre-terminal infections. I do not think that the hemorrhagic states of tuberculous meningitis are due to the tubercle bacillus, but to a secondary infecting organism.

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In reply to Dr. Spiller's discussion, I would state that I have presented two brains, one showing a rupture of the vein and the other showing a condition of osmosis without rupture of the vein, secondary to thrombosis of the cerebral sinus. I did not mean to imply, as Dr. Spiller suggests, that cerebral venous hemorrhage is always due to osmosis without rupture, but that it could be due to this cause.

November 12, 1908.

Periportal Fibrosis of the Liver in Tuberculosis.

By R. S. LAVENSON, M.D., and HOWARD T. KARSNER, M.D.

Tuberculosis has long been looked upon as a factor in the etiology of cirrhosis of the liver. Attention was probably first directed to their association by Brieger,[1] in 1879. Since then, the importance of this relationship has been emphasized by various observers—notably by Sabourin,[2] Hutinel,[3] Bäumler,[4] Bock,[5] Gougerot,[6] Mouisset and Bonnamour.[7] The French school has been especially prominent in according to tuberculosis a role second in importance only to alcoholism in the causation of hepatic cirrhosis.

While studying the histological sections of the organs of patients dying of tuberculosis, we were impressed with the frequency of the occurrence of minor degrees of perilobular fibrosis—changes that would not warrant a diagnosis of cirrhosis, but sufficiently marked to permit the recognition of a distinct structural alteration of the liver. We have tabulated our findings in fifty cases, which include tuberculosis of various organs and of all types. The majority are cases of pulmonary tuberculosis; though the list includes cases of acute miliary tuberculosis, and tuberculosis of the joints, bones, serous surfaces, and glands. We have classified the fibrosis, according to its degree, as slight, moderate, or marked.

Under the term slight are included those cases in which there was an undoubted, though not extensive, increase in the fibrous elements of the Glissonian capsule. In some cases this increase was limited to the periportal spaces; in others, it surrounded the entire lobule.

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In practically none of these cases was there any multiplication of bile canaliculi.

The instances designated as moderate are those in which the fibrosis was more definite than in the former class, yet not sufficient to approach in anywise the stage that would warrant the diagnosis of a distinct cirrhosis. Among these cases there was frequently found a moderate multiplication of bile canaliculi.

Those cases designated as marked present an extensive increase in the perilobular tissue, associated in the majority of instances, with a multiplication of the bile canaliculi. Though one hardly would be justified in diagnosticating the cases in this group as cirrhosis, the changes must be looked upon as differing not at all in kind, and very slightly in degree, from those typical of an atrophic cirrhosis.

In addition to these three grades of perilobular fibrosis, more or less intralobular fibrosis was observed in a few of the cases.

Compiling the results of the histological examinations of the 50 cases studied according to the foregoing classification, we found some degree of fibrosis present in 46; in other words, in 92 per cent. of the cases. In 14 cases, or 28 per cent., this fibrosis would be designated as slight; in 22 cases, or 44 per cent., as moderate; in 9 cases, or 18 per cent., as marked. In one case, or 2 per cent., the fibrosis was distinctly and almost exclusively of an intralobular type. Moreover, in 5 cases, or 10 per cent., of those classified as having some degree of perilobular fibrosis, there was, in addition, an intralobular fibrosis.

Realizing that the patients from whom these statistics were drawn—for the most part, inmates of the Philadelphia Hospital—were of a class in whom other causes of liver fibrosis are not uncommon, we have studied the sections of livers from 40 non-tuberculous patients, so selected as to conform to the cases in the tuberculous series in regard to the general hygienic surroundings, age, and the existence of arteriosclerosis.

In the non-tuberculous series we found some degree of fibrosis present in 54.5 per cent. of the cases, as contrasted with 92 per cent. in the tuberculous series. This fibrosis was slight in 32.5 per cent. of non-tuberculous cases, as compared with 28 per cent. in the tuberculous series; 17.5 per cent. of the cases in the non-tuberculous series

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were designated as exhibiting a moderate fibrosis; while in the tuberculous cases this class included 44 per cent. of the cases. The fibrosis was marked in 2.5 per cent. of the non-tuberculous series, as contrasted with 18 per cent. in the tuberculous series.

We have, furthermore, classified the cases in the tuberculous series in regard to alcohol. In 44 per cent. of the cases there was no mention made of the use or the abuse of alcohol. In 26 per cent. of the cases there was abstinence from alcohol. In 24 per cent. of the cases it was taken in moderation; and in 6 per cent. there was abuse of alcohol. We feel justified in expressing the opinion that these percentages do not indicate a greater abuse of alcohol than ordinarily exists in the type of patients from whom both of our series were drawn.

A consideration of the statistics that we have presented leads us to the conclusion that the milder degrees of perilobular fibrosis of the liver, are more frequently met with in tuberculous than in non-tuberculous individuals. These changes differ only in degree from those that constitute the histological characteristics of hepatic cirrhosis.

Stoerck,[8] in experimental tuberculosis in guinea-pigs, encountered this same frequency of liver change. He found that the injection of virulent tubercle bacilli, or attenuations of the same, into guinea-pigs, regularly produced a perilobular fibrosis, presenting the characteristics of a true cirrhosis. Hansemann[9] showed also that spontaneous tuberculosis in rabbits more or less consistently induces hepatic fibrosis; and Brieger, before the discovery of the tubercle bacillus, observed similar changes after the injection of tuberculous material into rabbits and guinea-pigs. Both clinically and experimentally, the perilobular rather than the intralobular cirrhosis has been the form that has most commonly been found associated with tuberculosis. Baumler, and later, his pupil, Bock, called attention to the association of a hypertrophic cirrhosis with tuberculosis. In a considerable percentage of the cases they looked upon the tuberculosis as secondary to the cirrhosis; but in numerous instances they took the reverse to be true. In but one case, as has already been mentioned, did we find the fibrosis to be almost exclusively intralobular. In 10 per cent. of the cases, however, there was a

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moderate degree of intralobular fibrosis, associated with a perilobular fibrosis.

What the pathogenesis of these changes is, we can but conjecture. Stoerck believes that in guinea-pigs there is first a localization of tubercle bacilli in the neighborhood of the capsule of Glisson. This casues necrosis of the parenchyma and proliferation of the connective tissue. Subsequently, the tubercle bacilli disappear, and the fibrous tissue already formed obstructs portal twigs, and thus leads to further necrosis and fibrosis. Whether this hypothesis is applicable to the changes in human beings, or whether they are the result of the action of the toxins of tuberculosis on the liver tissue, it is impossible to say. That tubercle bacilli have a ready means of access to the liver in many instances is shown by the fact that there was tuberculosis of some portion of the area drained by the portal vein in 48 per cent. of our cases; and in 38 per cent. of the cases there was coincident miliary or caseous tuberculosis in the liver. In those cases of fibrosis in which no tuberculosis is found in the parts drained by the portal vein, the liver changes may be the result of the action of the toxins of tuberculosis; or, if Rosenberger's[10] recent claims of a bacteriemia in tuberculosis are correct, there may be an actual localization of tubercle bacilli in the liver in all cases.

In conclusion we desire to emphasize that the changes we have described are not peculiar to tuberculosis; that they occur as a result of other factors is shown by the statistics we have presented of non-tuberculous cases. Our study, however, shows them to be more frequent in tuberculous than in non-tuberculous individuals; we therefore conclude that tuberculosis is one of the prominent factors in their causation. This harmonizes with the view held by some observers that tuberculosis is a frequent cause of cirrhosis of the liver which can be called the terminal stage of the liver changes which have served as the topic of our study.

The following list shows the general pathological diagnosis of the cases which made up our tuberculous series:

CASE I (979).—S. S., no age given, white, female.

Pathological Diagnosis. Calcified tuberculous nodule of lung; chronic adhesive pleurisy; chronic caseous and calcified tuberculosis of retroperitoneal lymph nodes; cholelithiasis; ulcerative enteritis;

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caseous tuberculosis of adrenals; fatty degeneration of kidneys; slight arteriosclerotic atrophy of kidneys; chronic fibrous myocarditis, moderate perilobular fibrosis especially of a periportal type, with fatty degeneration of liver.

CASE II (1137).—M. S., aged seventy-four years, black, male.

Pathological Diagnosis. Chronic ulcerative phthisis; chronic adhesive pleurisy; hypertrophy and dilatation of heart (right side); atrophy of left side; chronic hypertrophic gastritis; tuberculosis of intestines, mesenteric lymph nodes, tuberculosis of kidneys and chronic interstitial nephritis; moderate grade of perilobular fibrosis and miliary tuberculosis of liver.

CASE III (1059).—J. Y., no age given, white, male.

Pathological Diagnosis. Miliary tuberculosis of lung; caseous tuberculosis of liver and lymph nodes; chronic fibrous endocarditis; mixed leukemia and hyperplasia of spleen, lymph glands and lymph glands of liver; parenchymatous degeneration and lymphadenomata of kidney; arteriosclerosis; moderate perilobular fibrosis of liver.

CASE IV (1111).—A. V., aged fifty-six years, white, male.

Pathological Diagnosis. Tuberculous meningitis; chronic adhesive pleurisy; caseous tuberculosis of lungs; miliary tuberculosis of spleen; amyloid of kidneys and spleen; arteriosclerosis; moderate perilobular fibrosis of liver.

CASE V (1220).—J. C., aged fifteen years, white, male.

Pathological Diagnosis. Tuberculosis of left kidney and bladder; pyonephrosis of right kidney; chronic diffuse nephritis; acute pancreatitis and purulent cholecystitis; chronic interstitial splenitis and perisplenitis; chronic fibrous and purulent pleurisy; atelectasis and congestion of lungs; marked periportal fibrosis and miliary tuberculosis of liver.

CASE VI (975).—T. B., aged sixteen years, white.

Pathological Diagnosis. Tuberculosis of hip joint; miliary tuberculosis of lungs; chronic fibrous pleurisy; fatty degeneration of heart; amyloid of spleen, liver and kidneys; chronic diffuse nephritis; tuberculosis of liver, kidney, bladder and mesenteric lymph glands; slight periportal fibrosis of liver.

CASE VII (981).—T. M., aged nine months, white, female.

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Pathological Diagnosis. Early miliary tuberculosis of lungs; cloudy swelling of kidneys; fibrosis and hyaline degeneration of spleen; moderate perilobular fibrosis of liver.

CASE VIII (1149).—G. O., aged thirteen years, white, male.

Pathological Diagnosis. Chronic ulcerative tuberculosis of lungs; tuberculosis of kidneys, ureters, bladder, also spleen, intestines and appendix; chronic adhesive pleurisy; moderate perilobular fibrosis and miliary tuberculosis of liver.

CASE IX (1071).—M. T., aged thirty-nine years, black, female.

Pathological Diagnosis. Caseous tuberculosis of bronchial lymph nodes; calcified nodule in lung; chronic adhesive pleurisy; chronic fibrous valvulitis; chronic interstitial splenitis; chronic interstitial pancreatitis; no arteriosclerosis; practically no perilobular fibrosis of liver.

CASE X (1041).—C. B., aged two months, white, male.

Pathological Diagnosis. Tuberculous bronchopneumonia; tuberculosis of thoracic lymphatics, thymus, endocardium, intestines, spleen, liver, kidneys, and mesenteric lymph glands; chronic interstitial pancreatitis; very slight perilobular fibrosis, marked intralobular fibrosis and miliary tubercles of liver.

CASE XI (942).—C. G., white, male.

Pathological Diagnosis. Chronic ulcerative and caseous tuberculosis of lungs; chronic suppurative pleurisy of left side; chronic adhesive pleurisy of right side; subacute parenchymatous nephritis; tuberculous enteritis; caseous tuberculosis of mesenteric lymph nodes; moderate marked periportal fibrosis with considerable modification of bile ducts; slight chronic passive congestion of liver.

CASE XII (1496).—W. H., white, aged fifty-eight years, male.

Pathological Diagnosis. Fibrous tuberculosis of lungs; chronic adhesive pleurisy; purulent pericarditis; chronic interstitial splenitis with tuberculosis; tuberculous enteritis; chronic interstitial pancreatitis; chronic interstitial nephritis; arteriosclerosis; marked perilobular fibrosis; cirrhosis with multiplication of bile canaliculi of liver.

CASE XIII (1505).—E. M., aged forty-nine years, white, female.

Pathological Diagnosis. Acute fibrinous pleurisy; pneumonic phthisis; conglomerate tuberculosis of lung; fatty degeneration of

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heart; acute parenchymatous nephritis; chronic interstitial pancreatitis; marked perilobular fibrosis with extreme degree of fat infiltration of liver.

CASE XIV (1067).—A. T., aged sixty-one years, female.

Pathological Diagnosis. Tuberculous mediastinal lymph nodes and tuberculous pericarditis; healed tuberculosis of lungs; chronic adhesive pleurisy; chronic interstitial myocarditis, splenitis and nephritis; ossification of kidney capsule; arteriosclerosis; slight perilobular fibrosis of liver.

CASE XV (1011).—A. B., aged forty-six years, white, male.

Pathological Diagnosis. Caseous tuberculosis of lungs; chronic adhesive pleurisy; hypertrophy of heart; chronic interstitial splenitis; chronic interstitial pancreatitis; chronic interstitial nephritis; arteriosclerosis; moderate perilobular fibrosis of liver.

CASE XVI (1081).—C. K., aged seventy-nine years, white, male.

Pathological Diagnosis. Healed tuberculous foci at both apices; chronic endocarditis and myocarditis; chronic diffuse nephritis; chronic interstitial splenitis; arteriosclerosis; slight periportal fibrosis of liver.

CASE XVII (1099).—L. B., aged fifty-six years, black, male.

Pathological Diagnosis. Chronic ulcerative phthisis; chronic fibrous myocarditis and brown atrophy of heart; chronic adhesive pleurisy; fibrosis of pancreas; chronic interstitial nephritis; arteriosclerosis; moderate perilobular and intralobular fibrosis of liver.

CASE XVIII (960).—C. M., aged twenty-one years, white, male.

Pathological Diagnosis. Tuberculoma of liver, miliary tuberculosis of liver; bronchopneumonia and miliary tuberculosis of lungs; chronic adhesive pleurisy; chronic interstitial splenitis; chronic interstitial nephritis; chronic interstitial pancreatitis; no arteriosclerosis; tuberculosis of bronchial and abdominal lymph nodes, kidney and adrenal; marked perilobular and intralobular fibrosis and miliary tuberculosis of liver. Stained smears for caseous adrenals showed the presence of tubercle bacilli.

CASE XIX (868).—J. C., aged sixty-four years, white, male.

Pathological Diagnosis. Chronic ulcerative phthisis; chronic adhesive pleurisy; brown atrophy of heart, miliary tuberculosis of spleen; chronic interstitial nephritis; miliary tuberculosis of kidney;

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tuberculous enteritis; caseous tuberculosis of adrenal; tuberculosis of retroperitoneal lymph nodes; arteriosclerosis; marked perilobular and intralobular fibrosis and miliary tuberculosis of liver.

CASE XX (898).—R. R., aged twenty-four years, white, male.

Pathological Diagnosis. Chronic ulcerative phthisis; pneumonic phthisis; chronic adhesive pleurisy; chronic interstitial myocarditis; amyloid and tuberculosis of spleen; chronic interstitial pancreatitis; chronic parenchymatous nephritis; caseous tuberculosis of bronchial lymph nodes; moderate perilobular fibrosis and miliary tuberculosis of liver.

CASE XXI (1088).—M. G., aged twenty-three years, black, male.

Pathological Diagnosis. Chronic caseous tuberculosis of lungs; chronic adhesive pleurisy; conglomerate and miliary tuberculosis of spleen; caseous tuberculosis of kidney and chronic interstitial nephritis; chronic interstitial pancreatitis; slight perilobular fibrosis and miliary tuberculosis of liver.

CASE XXII (1075).—J. C., aged forty-seven years, white, male.

Pathological Diagnosis. Chronic ulcerative phthisis; chronic adhesive pleurisy; brown atrophy of heart; amyloid and tuberculosis of spleen; peptic ulcer; ulcerative tuberculosis of gut; chronic interstitial nephritis; no arteriosclerosis; well-marked, perilobular fibrosis and miliary tuberculosis of liver.

CASE XXIII.—J. H., aged forty-two years, white, male.

Pathological Diagnosis. Miliary tuberculosis of lungs; chronic myocarditis; chronic interstitial nephritis; tuberculosis, pyelonephritis and ureteritis; miliary tuberculosis of prostate; tracheal diphtheria; slight perilobular fibrosis and miliary tuberculosis of liver.

CASE XXIV (875).—C. G., aged forty-eight years, black, male.

Pathological Diagnosis. Miliary tuberculosis of lungs, liver, kidneys, adrenals, spleen and intestines; tuberculous pneumonia; caseous tuberculosis of bronchial, mediastinal and retroperitoneal nodes; chronic parenchymatous nephritis; very slight perilobular fibrosis and miliary tuberculosis of liver.

CASE XXV (927).—F. K., aged forty-three years, white, male.

Pathological Diagnosis. Chronic ulcerative phthisis; chronic adhesive pleurisy; brown atrophy of heart; chronic splenitis; cloudy

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swelling of kidneys; fibrosis of adrenals; moderate perilobular fibrosis and miliary tuberculosis of liver.

CASE XXVI (1497).—C. M., aged fifty-two years, white, female.

Pathological Diagnosis. Fibroid phthisis and caseous tuberculosis of lungs; chronic interstitial splenitis; chronic interstitial nephritis; moderate perilobular fibrosis of liver.

CASE XXVII (938).—E. B., aged fifteen months, black, female.

Pathological Diagnosis. Tuberculous pneumonia; miliary tuberculosis of lungs; tuberculosis of bronchial and mesenteric lymph nodes; tuberculous enteritis; acute parenchymatous nephritis; atrophy of heart; caseous tuberculosis of spleen; moderate perilobular fibrosis of liver with some multiplication of bile canaliculi.

CASE XXVIII (1468).—D. K., aged forty-eight years, black, female.

Pathological Diagnosis. General miliary tuberculosis of lungs and chronic adhesive pleurisy; chronic interstitial myocarditis; chronic interstitial splenitis and miliary tuberculosis of spleen; chronic interstitial nephritis; tuberculosis of mesenteric lymph nodes; arteriosclerosis; moderate perilobular fibrosis of liver.

CASE XXIX (859).—M. S., white, female.

Pathological Diagnosis. Bronchopneumonia; chronic myocarditis; miliary tuberculosis of spleen; chronic interstitial pancreatitis; chronic diffuse nephritis; tuberculous enteritis; tuberculosis of mesenteric and retroperitoneal lymph nodes; moderate perilobular fibrosis of liver.

CASE XXX (967).—M. B., aged thirty-one years, white, female.

Pathological Diagnosis. Chronic ulcerative phthisis; tuberculous bronchopneumonia; chronic adhesive pleurisy; fibrous myocarditis; tuberculosis and amyloid of spleen; tuberculous enteritis and colitis; amyloid kidney and liver.

CASE XXXI (1444).—H. K., aged thirty-four years, white, male.

Pathological Diagnosis. Pneumonic phthisis; chronic pleuritis; chronic parenchymatous nephritis; chronic perisplenitis and interstitial splenitis; fibrosis of pancreas; chronic interstitial myocarditis; no noticeable arteriosclerosis; moderate perilobular fibrosis and fat infiltration of liver.

CASE XXXII (879).—V. B., white, male.

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Pathological Diagnosis. Chronic ulcerative phthisis; chronic adhesive pleurisy; tuberculous enteritis; miliary tuberculosis of spleen, with amyloid; cloudy swelling of heart; moderately marked perilobular fibrosis of liver with moderate multiplication of bile canaliculi.

CASE XXXIII (1024).—K. B., aged thirty-one years, white, female.

Pathological Diagnosis. Chronic ulcerative phthisis and tuberculous pneumonia; chronic interstitial myocarditis and chronic valvulitis; chronic interstitial nephritis; arteriosclerosis; slight perilobular fibrosis of liver.

CASE XXXIV (1017).—T. M., aged twenty-two years, male.

Pathological Diagnosis. Acute miliary tuberculosis of lungs, liver, kidneys, and spleen; chronic proliferative tuberculosis of pleura and peritoneum; chronic adhesive pleurisy; chronic myocarditis; chronic interstitial splenitis; chronic parenchmyatous nephritis; moderate periportal fibrosis of liver.

CASE XXXV (1474).—W. B., aged sixty-four years, white, male.

Pathological Diagnosis. Tuberculous pneumonia; fibrous tuberculosis of lungs; fatty degeneration of heart and slight fibrosis; chronic interstitial splenitis and perisplenitis; chronic interstitial nephritis; arteriosclerosis; slight perilobular fibrosis of liver.

CASE XXXVI (1093).—A. C., aged fifty-eight years, white, male.

Pathological Diagnosis. Chronic ulcerative phthisis; chronic adhesive pleurisy; chronic interstitial nephritis; slight periportal fibrosis of liver.

CASE XXXVII (1498).—W. C., aged thirty-six years, white, male.

Pathological Diagnosis. Fibroid phthisis and miliary tuberculosis of lungs; chronic myocarditis; chronic interstitial splenitis; chronic interstitial pancreatitis; hydronephrosis; arteriosclerosis; chronic passive congestion of liver.

CASE XXXVIII (1105).—H. H., aged forty-three years, white, male.

Pathological Diagnosis. Chronic ulcerative phthisis; hypostatic pneumonia; chronic adhesive pleurisy; chronic interstitial splenitis; cyanotic induration of kidneys; arteriosclerosis; moderate perilobular fibrosis of liver with multiplication of bile canaliculi.

CASE XXXIX (882).—P. W., aged fifty-seven years, white, male.

Pathological Diagnosis. Chronic ulcerative phthisis; chronic adhesive pleurisy; hypertrophy of heart and chronic valvulitis;

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chronic perisplenitis; chronic interstitial nephritis; arteriosclerosis; slight but distinct perilobular fibrosis of liver.

CASE XL (1014).—S. C., aged twenty-five years, white, female.

Pathological Diagnosis. Chronic ulcerative phthisis; tuberculous bronchopneumonia; chronic adhesive pleurisy; chronic interstitial splenitis; cyanotic induration of kidneys; amyloid of spleen and liver; no arteriosclerosis; moderate perilobular fibrosis and chronic passive congestion of liver.

CASE XLI (2131).—H. F., white, male.

Pathological Diagnosis. Chronic interstitial myocarditis; hypertrophy and dilatation of heart; chronic aortic and mitral valvulitis; arteriosclerosis; chronic adhesive pleurisy; chronic ulcerative tuberculosis of lungs; tuberculous enteritis; fatty metamorphosis and cirrhosis of liver; acute splenic tumor; abscess of kidney with chronic passive congestion; chronic catarrhal cystitis; liver shows moderate perilobular fibrosis and considerable postmortem degeneration of parenchyma.

CASE XLII (1653).—J. D., aged seventy years, white, male.

Pathological Diagnosis. Chronic pleurisy; hydrothorax; pulmonary congestion and edema; apical tuberculosis and cicatrices of lungs; fatty degeneration of heart and chronic myocarditis; aortic and general arteriosclerosis; acquired diverticula of descending colon and sigmoid flexure; pancreatic congestion and hemorrhage; chronic diffuse nephritis; moderate perilobular fibrosis and miliary tuberculosis of liver.

CASE XLIII (1580).—P. C., aged fifty-two years, white, male.

Pathological Diagnosis. Miliary and conglomerate tuberculosis of lungs; dilatation of heart; chronic valvulitis (mitral and aortic); chronic interstitial splenitis; arteriosclerosis; moderate perilobular fibrosis and extreme fatty infiltration of liver.

CASE XLIV (2259).—J. B., aged forty-four years, black, male.

Pathological Diagnosis. Chronic adhesive pleurisy; chronic ulcerative tuberculosis, chronic fibroid tuberculosis of lungs and tuberculous bronchopneumonia; passive congestion of spleen; chronic parenchymatous nephritis, fatty cirrhosis of liver; edema and congestion of brain; slight perilobular fibrosis and fatty infiltration of liver.

CASE XLV (2145).—J. C., aged thirteen years, black, male.

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Pathological Diagnosis. Chronic ulcerative tuberculosis of lungs; chronic adhesive pleurisy; congestion and cloudy swelling of liver; chronic interstitial splenitis; subacute parenchymatous nephritis; tuberculous enterocolitis; tuberculous appendicitis; arteriosclerosis; moderate perilobular fibrosis and miliary tuberculosis of liver.

CASE XLVI (2239).—H. Z., aged twenty-one years, white, male.

Pathological Diagnosis. Fungus cerebri; tuberculous meningitis; chronic ulcerative phthisis; acute miliary tuberculosis of lungs; chronic adhesive pleurisy; cloudy swelling of myocardium; acute miliary tuberculosis of spleen; subacute parenchymatous nephritis; chronic passive congestion; slight perilobular fibrosis and miliary tuberculosis of liver.

CASE XLVII (859).—M. S., white, female.

Pathological Diagnosis. Bronchopneumonia; chronic myocarditis; miliary tuberculosis of spleen; chronic interstitial pancreatitis; chronic diffuse nephritis; tuberculous enteritis; tuberculosis of mesenteric and retroperitoneal lymph nodes; moderate perilobular fibrosis of liver.

CASE XLVIII (1006).—W. M., no age given, white, male.

Pathological Diagnosis. Chronic encapsulated and caseous tuberculosis of lungs; chronic fibrous perisplenitis; chronic adhesive pleurisy; chronic interstitial nephritis; marked perilobular fibrosis of liver, especially marked in periportal areas.

CASE XLIX (1403).—C. R., aged twenty years, black, female.

Pathological Diagnosis. Acute general miliary tuberculosis (most marked in the lungs and meninges); slight bilateral hydronephrosis; gravid uterus; chronic fibroid valvulitis; chronic adhesive pleurisy; tuberculous meningitis; slight perilobular and intralobular fibrosis of liver.

CASE L (1094).—K. H., aged thirty years, white, female.

Pathological Diagnosis. Chronic adhesive pleurisy; chronic myocarditis; chronic interstitial splenitis; chronic interstitial pancreatitis; amyloid of liver and spleen and kidney; chronic parenchymatous nephritis; no arteriosclerosis.

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Discussion.

Dr. Warfield T. Longcope: I should like to ask whether in any of the cases there were areas of caseation or any old tubercles in the connective tissue; also, whether the increase in connective tissue was diffuse or irregular and more or less localized. It is not infrequent, in cases of chronic tuberculosis, to find old chronic tuberculosis of the perilobular connective tissue; but it is not a general disease of the periportal connective tissue, but a localized condition. I have in mind a case in which the change in the periportal connective tissue was so marked as to be easily seen in the gross. It looked like a beginning cirrhosis of the liver; but it was localized, and not general, as in periportal cirrhosis.

Dr. C. Y. White: I should like to ask whether this fibrosis was part of a general fibrosis of the patient, or merely one localized to the liver. In examining specimens at the Phipps Institute, we find that almost all organs show fibrosis of some parts. It does not seem to me that the fibrosis is marked enough to be called cirrhosis. In chronic pulmonary tuberculosis, fibrosis is far more marked in the thyroid gland and in the adrenals than I have ever found it to be in the liver. It is likewise marked in the kidneys.

Dr. A. O. J. Kelly: If what I say seems adverse to the conclusions of Drs. Lavenson and Karsner, it must not be construed as depreciatory of their work, which is really excellent and concerns a most important subject. The first and second grades of the fibrosis exhibited in their sections and photomicrographs is not, I believe, in excess of that which occurs in the liver in many conditions in no way related to tuberculosis, such, for instance, as all fatty livers, of which the picture of the first grade of fibrosis is a good example. Indeed, I am inclined to believe that the first and second grades of the fibrosis may be detected in many livers that most of us would look upon as quite normal, and perhaps the third grade of the fibrosis might also be encountered here and there in really normal livers. That, however, certain grades of fibrosis may be found in many conditions does not preclude the possibility of the fibrosis being due to any one of them. Granting, then, that the fibrosis occurs in

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some cases of tuberculosis, the question to be determined is whether it is due to the tubercle bacillus, and if so, in what manner it arises. What I believe to be a noteworthy omission from Drs. Lavenson and Karsner's paper is the absence of mention of the condition of the parenchyma, which is of prime importance in all forms of hepatic fibrosis, including true cirrhosis; that is, it is important to know whether the changes in the interstitial tissue are primary or merely a replacement fibrosis. Furthermore, many tuberculous subjects consume considerable alcohol, despite repeated denials thereof; and the more one studies the antecedent factors in the ordinary or portal cirrhosis, the more he will find conclusive evidence of the influence of alcohol, although, of course, the alcohol may not act directly on the liver; perhaps similar conditions obtain in the fibrosis under discussion. Again, most tuberculous subjects suffer much with digestive disorders, in which enterogenic toxins are produced, or are, at least, not detoxified, and being transported to the liver may set up more or less well marked cirrhosis. The occurrence of fibrosis, as well as of cirrhosis, of the liver in tuberculous subjects, then, can very well be explained, certainly in the very great majority of cases, without recourse to any supposititious influence of the tubercle bacillus. That the tubercle bacillus, however, may be the causative factor cannot be denied; but an additional objection to this likelihood is the fact that the tubercle bacillus is rarely, if ever, primarily sclerogenous; that is, it does not give rise primarily to the formation of new connective tissue, although, of course, this often follows other tuberculous lesions.

DR. DAVID RIESMAN: I agree with Dr. Kelly that any communication that promises to throw light on cirrhosis of the liver is most welcome, and I hope that the paper we have just heard will stimulate further researches in this field.

One statement made by the authors surprised me, namely, that in only 6 per cent. of their cases had there been a history of alcoholism. I should say that that was exceedingly low for Blockley. We have been accustomed in the past to find there a much larger percentage, especially among patients suffering from tuberculosis. No doubt there is, as the microscopic sections indicate, a slight degree of fibrosis of the liver present, but whether it is dependent

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upon the associated tuberculosis is not easily determined. It would be necessary to make sure that the cases had not been alcoholic. I am not convinced, however, that alcohol is the chief factor in the etiology of ordinary cirrhosis of the liver. It is not impossible that some other toxic substance, or even a germ, is the real causative agent. Adami some years ago claimed that the cause was an attenuated form of the bacillus coli, but that is not believed, and I think he himself has recanted. Upon the hypothesis that cirrhosis is perhaps in itself a tuberculous process, I had Dr. Rosenberger make some investigations, about which he may have something to say. So far as we have gone no results have been attained. That cirrhosis of the liver predisposes to tuberculosis is, of course, a well-known clinical fact.

DR. R. C. ROSENBERGER: About two years ago I gave the results of the examinations of sixty-two livers removed from tuberculous subjects. The microscopic sections of these showed tubercles in over eighty per cent. The most constant change was marked congestion. Fatty infiltration was a frequent change, but only a few showed fibrosis. Whether this fibrosis, when present, was perilobular or intralobular, I do not know, as I did not pay marked attention to this point. We took the markedly atrophic cirrhotic livers, macerated the organs, made a suspension in normal salt solution, and injected it into guinea-pigs. No animal showed evidence of tubercle formation.

DR. ULLOM: I recently examined about one hundred livers histologically, and found about seven in which the fibrosis was marked. In two, it was true atrophic cirrhosis. One of these patients had given a history of syphilis and alcoholism; the other, of alcoholism alone. I remember seeing a number of cases that looked like those of Drs. Karsner and Lavenson, but I did not consider the fibrosis marked enough to put it down. I agree with Dr. Rosenberger that marked congestion is common; and I found the same percentage of livers with tubercles as he did—about 79 or 80 per cent.

DR. KARSNER, closing: We did not intend to imply that the changes present were those of true cirrhosis of the liver, but merely that there was a distinct perilobular fibrosis of these three degrees. The series includes no cases of true cirrhosis, though some of the

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marked cases of fibrosis were almost of that grade. Of course, among the cases that we included under the head of slight fibrosis there were probably some in which the personal equation entered into the consideration to a large extent. In these instances Dr. Lavenson and I first reached an agreement, and then referred them to Prof. A. J. Smith for his opinion. It was only after considerable study of such cases that we decided to include them.

In reply to Dr. Longcope's questions, I would say that the idea that definite tubercles are, in a sense, causative of fibrosis was well brought out in Stoerck's article. His examinations covered the livers of several hundred guinea-pigs, the animals having been killed at varying intervals after the injections of living cultures of tubercle bacilli into the peritoneum. He built up a series of pictures in this way, in order to determine the histogenesis of the experimental cirrhosis in these animals. In studying our cases, we thought that we might be able to work out something of the same sort; but the most careful search showed nothing to warrant the belief that the same process occurred in human livers. The miliary tubercles were scattered throughout the pulp, and occasionally were discovered out in the capsule of Glisson.

About the localization of the fibrosis we cannot say a great deal, because we did not make a great number of sections from one liver. However, as the livers were selected from a wide range of cases, we believe that the fibrosis was general.

Dr. White spoke of the association of fibrosis of the liver with fibrosis in other parts of the body. In the paper we mentioned the fact that in selecting our control series, we considered the presence of a general fibrosis in connection with fibrosis of the liver. In some of our cases there were to be found, according to the notes on the autopsy, no reference to an arteriosclerosis, to a chronic interstitial or parenchymatous nephritis, or to fibrosis in other organs.

Dr. Kelly's suggestion about the involvement of the parenchyma brings to my mind the very common presence of fat in the liver of tuberculous subjects. The rich fat diet that tuberculous patients usually take at the present day is sufficient to cause various grades of so-called fat infiltration, that lead to confusion and to exclude any positive deductions concerning parenchymatous changes. There

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are differences of opinion about fat infiltration and fatty degeneration; but, accepting the common differentration between the two, we are convinced that the fat found was largely the result of the rich fat diet. In a certain sense, the association of the fat conditions, some of which may be degenerative, with the mild grade of perilobular fibrosis, might be sufficient to make the condition a chronic diffuse hepatitis. The fatty change and the fibrosis might be originally caused by the same influences—the toxins of the tubercle bacilli or the bacilli themselves.

The question of perilobular and intralobular fibrosis is so confused that we made no attempt to differentiate the causes, but merely to draw attention to the comparative infrequency of intralobular fibrosis as compared with perilobular. So far as the cause is concerned, we must wait until later experiments are carried out in order to learn whether or not there is a true bacteremia in this condition. In the latter case, it will be a question as to how far the bacilli are instrumental in inducing the condition, as they did in Stoerck's series of guinea-pigs.

Dr. Riesman's suggestion that the number of alcohol abusers is low for the Philadelphia Hospital cases is true in itself, but we think that we have obviated criticism from this source in that the cases of the control series were selected from the same class of people as the cases of the tuberculous series, and alcohol would have approximately the same influence over the control cases as the tuberculous cases.

Dr. Riesman also said that he believed that in some cases cirrhosis of the liver predisposes to tuberculosis. I can point out to him a reference in the body of our paper to some work by Bäumler and Bock, in this connection. In the early 80's, they raised the question whether the tuberculosis or the cirrhosis was the primary condition. They considered true cirrhosis, rather than perilobular fibrosis as primary, and came to the conclusion that some of the cases of tuberculosis were probably predisposed to the disease by the cirrhosis, and that the liver cirrhosis was sometimes subsequent to tuberculous infection.

To Dr. Rosenberger and Dr. Ullom, I would say that we did not mean to include in the series cases of well-marked cirrhosis. Our

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studies were limited to the production of mild changes that might or might not have led up to cirrhosis.

DR. R. S. LAVENSON, closing: Dr. Karsner and I became interested in the findings that we have described while doing a large number of autopsies at the University and Philadelphia Hospitals. Examining the histological specimens from these autopsies, we soon became impressed with the frequency of minor degrees of periportal fibrosis in tuberculosis. At the time, neither of us knew of the importance ascribed by various writers to tuberculosis in the causation of hepatic cirrhosis. I believe that the personal factor as to what one would consider minor degrees of periportal fibrosis is the cause of the difference of opinion existing between ourselves and the gentlemen who have preceded us. That we have been more critical than most observers is, I think, well shown by the frequency with which we have found these minor changes in non-tuberculous patients. I am very confident that livers presenting these histological features cannot be looked upon as normal. Moreover, I feel that those who think that other factors than tuberculosis may be responsible for the changes that we have described must recall that in animal experiments, such as those of Stoerck, tuberculosis can be looked upon as the only factor present; and varying degrees of periportal fibrosis were consistently found in the livers of these animals.

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SYMPOSIUM ON CHILDHOOD PATHOLOGY.

Antenatal Pathology.

By B. C. HIRST, M.D.

THE death rate of the nine months of intra-uterine life is the highest of any period of the same length in man's existence. For every three or four deliveries at term there has been at least one miscarriage, and if one adds the stillbirths at term to this percentage, it is obvious what an appalling mortality characterizes this brief space in human life. The pathology of the embryo and fetus, therefore, is worthy of study, with a view to decreasing a waste of life that has the greatest sociological importance; but the subject presents so many difficulties and this study yields so little of practical importance that the busy practitioner in his press of work has little leisure to devote to it. It is, besides, an immense field, and I can do nothing more this evening than to present a brief sketch of a few of its more important practical problems. Syphilis of the embryo, the mechanical causes of malformations, the influence of maternal impressions on the psychological and physical development of the fetus, are the subjects that are most profitable and interesting to discuss.

The facts in regard to syphilis which the practical physician should keep in mind are the length of time after infection that conception should be avoided, the possibility of infecting the fetus by syphilis acquired during pregnancy, and the diagnostic signs of the disease in the dead fetal body or in the living syphilitic infant. Four years under treatment is agreed upon as the proper period to insist upon before a man with syphilis should marry, or either parent risk the production of children. The painful duty sometimes devolves upon a physician to violate professional confidence in order to inform the innocent party of the danger incurred should a man insist upon marriage despite his infection. It has been claimed that syphilis acquired during pregnancy is not transmitted to the fetus, but this is not true. In a large proportion of cases the fetus is infected. It is necessary to make the diagnosis of fetal or infantile syphilis from evidences in the fetal body or from clinical signs in the living

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infant without questioning the parents too closely or without opening the door of a very ugly skeleton closet. This can be done by the discovery of the Spirocheta pallida, by Wegner's sign, by enlargement of the liver and spleen, by connective-tissue overgrowth, and by the skin eruptions and other clinical manifestations of congenital syphilis. Occasionally one is chagrined to find that what he regarded as diplomacy or discretion on his part in making the diagnosis without asking questions of the parents is entirely unnecessary, as they are fully aware of the existence of the disease in one or both of them.

Experimental studies in the lower animals demonstrate the possibility of producing malformations in the embryo by traumatism or succussion. It may be the duty of the physician to warn his patients of this danger. I have seen malformed and idiotic children the results of attempts on the part of the mother to induce abortion.

Finally the effect of maternal impressions upon the mother is a fascinating subject that might lead to endless indulgence in speculation and argument. In this brief summary it is sufficient to emphasize only one or two points. I think that there can be no dispute that violent emotions in the mother can affect the mentality of the child, can influence its psychology in the future, and can even arrest its physical development or terminate its existence. I know of a woman who gave birth to a succession of idiot children because her husband, though not an habitual drunkard, got beastly drunk on his wedding night. We all remember the dread of a naked sword exhibited by King James, imputed to the murder of Rizzio, before the eyes of his pregnant mother. We also recall the famous case of Jesse Pomeroy, the homicidal maniac, whose mother, during her pregnancy, took delight in watching the slaughter of animals. A recollection of Barker's interesting account of the transmission of Lord Dundreary's ridiculous skip to the offspring of the young girl who was enamored of him will be recalled by those of us who had the good fortune to hear him tell it. But the photographic reproduction of a physical defect in an infant of some impression upon the mother during pregnancy is a different matter. This is a deeply imbued superstition among the laity, productive often of great distress of mind, which it is our duty to combat. How tragic such a belief may prove

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is illustrated in the case of a pregnant woman who visited an exhibition of the dipygus parasiticus, Laloo. She was so convinced that her fetus would display a similar deformity, owing to the deep impression made upon her by this monster, that upon returning home she threw herself out of the window. The postmortem examination showed a normally developed fetus in her womb.

February 25, 1909.

Infections of the Newborn.

By SAMUEL McC. HAMILL, M.D.

Under this heading, I shall consider the localized infections of the umbilical stumps and sepsis in the newly born.

Localized Infections of the Umbilical Stump. It is very difficult to bring about dessication and shedding of the umbilical stump in an entirely aseptic manner. The drying tissues form such a good medium for the development of microörganisms that the most careful protective measures cannot free it entirely of bacteria. Mild infections are, therefore, common during this process.

One frequently notes a slight serous or seropurulent discharge, with or without redness, which is usually the product of an infecting organism. These mild degrees of omphalitis may develop into the severer forms and produce inflammatory lesions of considerable extent, involving the subcutaneous tissues and associated with quite profuse discharge of pus.

These lesions may extend farther and involve the umbilical vessels, producing arteritis and phlebitis. The extension usually occurring through the sheath of the vessels, passes on to the lymphatics, thus producing a periarteritis, from which the vessels may become inflamed with the production of thrombi. Less commonly, the infection is direct and there occurs a primary arteritis or phlebitis.

The lesions of arteritis may vary in degree from those which are mild and scarcely manifest to extensive inflammation of the vessels and perivascular tissues. The entire vessel or only a portion of it may be involved, or more rarely the reaction may be purely perivascular.

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The vessels may be thick and firm, dilated throughout their course or sacculated here and there.

The vessel walls are thickened, the intima is often partially destroyed, and the clots are of a cheesy consistence, or, having broken down entirely, are converted into pus, which may fill the entire lumen of the vessel. In these far advanced types, there may be an extension of the process to the peritoneal cavity, with the corresponding pathological changes and the evidences of septicemia, which will be discussed later. Involvement of the veins, which is not as common as that of the arteries, gives less superficial evidence of its existence. The autopsy usually shows the vein involved in its entire length and filled with pus and septic thrombi. The phlebitis may extend and involve the portal vein and its branches, and the liver may be the seat of generalized hepatitis or multiple abscess formation.

Sepsis in the Newly Born. These lesions are frequently but preliminary to *sepsis in the newly born*. The clinical course of these generalized infections varies in degree as does that of the specific infections of later childhood or adult life, depending upon the virulence of the infecting organism or the individual resistance of the infant. Such clinical variations have led to attempts to classify these infections, from which efforts Winckel's disease, Buhl's disease, and melena neonatorum have been evolved.

The complex of symptoms in Winckel's and Buhl's diseases are identical with those which may occur in the course of severe infections with any one of a number of different microbes, and their pathological picture is that of infection. There is no basis, in short, for their existence, and they should be eliminated from the catalogue of diseases.

Melena neonatorum is not a disease, but a symptom, and most often a symptom of some infection. Many theories have been advanced to explain its etiology, such as congestion and ulceration of the gastro-intestinal tract, autodigestion of the gastric mucosa, alterations in the brain from injuries at birth, diseases of the liver, congenital lesions of the heart, deficiency of fibrin in the blood of the newly born, chemical alterations of the blood, the delicate structure of the bloodvessels in early life, premature birth, precipitate labor, prolonged labor, too early and too late tying of the cord, plethora, asphyxia, passive hyperremia, congestion of the mesenteric arteries, congenital syphilis,

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hemophilia, diseases in the mother, such as anemia, eclampsia, Bright's disease, tuberculosis, alcoholism, plumbism, and various other diseases which, like syphilis, produce sclerotic changes, and, finally, some form of infection.

Which of these may be considered the most important depends much upon which author one follows. Eliminating infection, none of them seems adequate to explain the instances of widespread hemorrhage which one frequently sees, unless it be syphilis and those relating to chemical alterations in the blood.

Mraczek, Esser, Kundrat, Lequex, and Knopfelmacher have each demonstrated the occurrence of melena in infants, in whom they believed all possible causes but syphilis had been excluded. Lequex, however, distinctly states that he considers syphilis an exceedingly rare factor, save in its predisposing relationship. It is my belief that it is only in this predisposing relationship that the various causes mentioned act, if they act at all, and in support of this view, I would emphasize these points: (1) That much of the pathological data upon which these theories have been based antedated the bacteriological investigation of these cases; (2) that anërobic cultures have rarely been made on the cases which have been reported as negative to bacteriological investigation; and (3) that, in the instances in which complete bacteriological studies have been made, the vast majority have shown some form of infection, and the pathological picture has been that of sepsis.

In Lambert's recent report of the extraordinarily interesting case of hemorrhage in the newly born, in which a practically moribund infant was restored within a few hours to a state of perfect health, as the result of direct transfusion, he says, regarding the etiology: "The latest accepted theories point not to ulceration or gross lesions, but to the capillary bloodvessels as the seat of the bleeding, and the clinical picture of these cases is undoubtedly very like that of an infection as the etiological factor. But the course and the remarkable cure of the case reported here would seem to disprove both the infectious theory of its origin and the bloodvessel explanation, etc." In reviewing the facts of the case, he says: "Hemorrhages and fever began simultaneously; normal temperature was reached forty hours after the onset of fever, but the hemorrhages became progressively worse for

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three days after all fever had disappeared. At the time of the operation, the baby was in perfect health. . . . The only possible explanation of so rapid a change must be found in a chemical condition of the blood, and the final conclusion as to the nature of the disease is that melena neonatorum is a congenital malformation of the blood of unknown chemical nature."

With these conclusions I do not agree. In the first place, there is no evidence in his report to show that a possible infection was excluded by bacteriological studies; in the second place, the clinical history points strongly to a disease of infectious origin; and, in the third place, the pathological picture of hemorrhage and congestion is present in practically all infections of the newly born. In the rarest instances only is there not found some degree of hemorrhage into some organ of the body, even though it may be but microscopic.

Sufficient experimental evidence has been adduced to show the etiological relationship of bacillary infection to hemorrhage. Hemorrhages have been produced in various animals—dogs, rabbits, guinea pigs, pigeons—by the injection of a number of different microörganisms (Gaertner's bacillus, the diphtheria bacillus, Bacillus pyocyaneus, Friedlander's bacillus) (Gaertner, Roux and Yersin, Langlois and Charrin, Roger), as well as by the injection of soluble bacterial toxines (Langlois and Charrin).

We do not as yet, it is true, understand the modus operandi by which these organisms and their toxins produce hemorrhages, nor have we explained the differences in degree of the hemorrhages in different cases.

This latter probably bears direct relationship to the virulence of the infection or to the nature of the infecting organism; but, to apply Lambert's theory of the "chemical condition of the blood," it may be that the toxins resulting from the bacterial infection bring about such chemical alterations which, possibly affecting its coagulability, and admitting of free osmosis in the capillary vessels, results in the production of the widespread hemorrhages which sometimes occur in these cases. The rapid transformation which occurred in Lambert's case—practically from death to a normal state—would result just as readily were the chemical alteration the result of a bacterial infection as if it were dependent upon some congenital malformation.

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The striking results reported by Delestre, in which, to use his own words, he observed "infected infants, cyanosed, cold, and practically moribund, resuscitated positively under his eyes" during the withdrawal of a few cubic centimeters of blood, and the instance which I have reported, in discussion, of a deeply cyanosed, jaundiced, dyspneic, feverish, practically moribund, newborn infant, with a streptococcic infection, relieved instantly of all disturbing symptoms and within a few hours restored to perfect health by the withdrawal of 2 c.c. of blood, emphasize the remarkable closeness of the balance between fatal intoxication and health and render the theoretical exclusion of a bacterial origin in Lambert's case untenable. The accumulating evidence, as I have already stated, points strongly to an infectious origin for these cases.

In the light of our present knowledge, however, probably the safest conclusion to draw is that some of the various factors mentioned—especially congenital syphilis—may occasionally produce true melena; that they act more frequently as predisposing factors, but that in the majority of instances melena is a symptom of some form of infection.

Attempts by Gaertner, Klebs, Eppinger, and others to isolate a specific organism in cases of melena, naturally failed. These infections of the newborn, of which melena is a symptom, may be caused by any one of a number of different microörganisms. Those most commonly encountered are the so-called pyogenic forms—the Staphylococcus albus and aureus, and the streptococcus in its various strains. Besides these, the Diplococcus pneumoniæ (Fränkel-Weichselbaum), the Bacillus coli communis, the Bacillus pyocyaneus, the gonococcus, the influenza bacillus, the bacillus of Friedländer, the meningococcus, Eberth's bacillus, the bacillus of Babés, the Bacillus hemorrhagica of Klebs, the encapsulated bacillus of Dungern, and the diphtheria bacillus have been isolated by various investigators.

It is impossible to determine the variety of infecting organism in the individual case, except by its isolation from the blood during life or by its recovery at the autopsy. Even then, as experience has shown, the results may be negative unless anaërobic as well as aërobic cultures are made.

Susceptibility to Infection. It is generally supposed that newborn infants possess a relatively low resistance to septic infection,

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which may or may not be true. It is quite certain that those prematurely born and the badly nourished are relatively more susceptible than the normal newborn. Theoretically, the desiccation and shedding of the umbilical stump, and such physiological processes as the early desquamation of the skin and mucosa, and the undeveloped condition of the lymphatic system, would seem to throw wide the portals of entry.

On the other hand, these infections are of rare occurrence, except in institutions, and, owing to the enforcement of strict aseptic measures, of rapidly decreasing frequency even in them. Is it not, therefore, in part a question of the severity of the exposure as well as the resistance of the infant?

Indeed, when one considers the possibilities of infection for the newborn, one is almost inclined to feel that its resisting power is relatively great. In the first place, there exists the possibility of intrauterine infection—a number of instances of which have been recorded. Following this, the passage through the birth canal, which is always accompanied by some degree of traumatism and new exposure, suddenly places the infant in a new environment of greatly lowered temperature, he vigorously breathes in the new atmosphere with its contents, he passes through the necessarily contaminated hands of the accoucher and nurse, and is wrapped in garments which may be macroscopically clean, but are not aseptic.

The bath follows, the cord is dressed and redressed from day to day. The nipples of the mother, which are difficult to protect and which may be the seat of erosions, are brought frequently in contact with the delicate mucosa of the infant's mouth; but, notwithstanding this extensive exposure, infection is relatively rare and mainly limited to hospital practice.

When, therefore, one compares the liability to exposure with the proportionately small number of cases of infection, one cannot but feel that too great stress may be laid upon the question of reduced resistance.

Portals of Entry. The avenues through which the bacteria gain entrance to the organism are: The placental circulation, the umbilical stump, the skin, the alimentary canal, the respiratory tract, and less often the ear, conjunctiva and genito-urinary tract. For reasons

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already mentioned, it is clear that infection by the umbilical cord is common.

However, one cannot accept the presence of suppurative lesions of the cord or even the presence of thrombi in the umbilical vessels as final proof that the cord has been the channel of infection. The generalized infection may have entered through another portal, because it has been clearly shown that such lesions of the cord frequently exist without the production of generalized sepsis.

The skin, owing to its great surface, its physiological peculiarities, its tendency to specific inflammation, and its liability to trauma, often admits infecting organisms. The great frequency with which older institutional infants become septic secondarily to even the milder forms of eczema clearly points out that the defensive power of the skin against the entrance of microörganisms is very easily disturbed.

There are definite instances recorded in the literature of the direct transmission of infection from infant to infant by the use of the same bath water, bathing cloths, and bathtubs, and bacteriological studies of the water in which these infants have been bathed have shown the presence of microörganisms which are held responsible for these infections. The experience of the Maternity Hospital of the University of Pennsylvania and the Preston Retreat, in practically eliminating the late infections of the newborn by the introduction of sterilizable porcelain bath tubs, taken with the facts just mentioned, not only emphasize the importance of proper aseptic technique in bathing these infants, but point out clearly the importance of the skin as an avenue of infection.

The mucosa of the alimentary tract undergoes certain physiological changes after birth, which tend to make it readily permeable to bacteria. When one considers its exposure to bacterial infection, it is easy to understand why the alimentary tract plays a conspicuous role in the introduction of these infections. The resting of infected particles on the mucous membranes of the upper air passages from the inhaled air, the danger of introduction into the mouth of an infected nipple, the swallowing of an infected milk, the careless cleansing of the mouth, which may lead not only to the introduction of infected material, but to traumatism, and various other sources of infection, make this point clear.

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Confirmation of the frequency of this avenue of infection rests in the fact that the early symptoms are commonly in the intestinal tract, and, as Lequex has pointed out, the pathological manifestations point to infection through the portal circulation.

The respiratory tract was formerly thought to be an even more common channel of infection, a view which was largely based upon the frequent occurrence of what was supposed to have been aspiration pneumonia. Pneumonia from aspiration of infected particles probably occurs at times, but the fact that extreme dyspnea and cyanosis exist in many of these cases without associated pulmonary lesions, together with the character of the lesions found at autopsy, would indicate, on the one hand, that they cannot be diagnosticated clinically, and, on the other hand, that the pneumonias which develop are most often the result of blood infections.

The *pathological changes* are, briefly, congestion, hemorrhage, and parenchymatous degeneration. Hemorrhages, either microscopic or macroscopic, and congestion are present in most of the internal organs. They may be found also in the skin, the eye, the brain and its membranes, and the bone marrow. Hemorrhage into the individual organs may be quite extensive; in a number of instances it has led to rupture of the suprarenal capsule. Large subdural hemorrhages have been noted, as well as encephalitis, meningitis, and abscess of the brain.

The *lungs* are frequently the seat of hemorrhagic infarcts, embolic abscesses, small patches of bronchopneumonia, often scarcely demonstrable to the naked eye. Congestion is always present. The *pleuræ* may be inflamed and contain a hemorrhagic exudate.

The *heart* rarely shows changes in the valves. Fatty and parenchymatous changes in the muscle are common. The *pericardium* is occasionally inflamed and may contain a bloody effusion. The *gastro-intestinal* tract frequently contains clotted blood. The mucosa of the stomach and intestines may be congested to any degree; it may be the seat of small ulcerated areas which are presumably the product of embolic processes. Hemorrhages of varying degree, involving the mucosa or serosa, are frequent.

The *liver* usually shows the most marked changes, such as, parenchymatous or fatty degeneration, hepatitis, and multiple abscesses. The *kidneys* may be the seat of parenchymatous changes, fatty degen-

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eration, hemorrhages, and interstitial inflammation. The pelvis is sometimes involved.

It is seen from what has been said that there are no specific pathological lesions produced by these infections. They are the same that may result from any of the acute infectious diseases in early life.

February 25, 1909.

A Consideration of the Pathological Anatomy and Pathogenesis of Status Lymphaticus in Children.

By JOHN HOWLAND, M.D.[1]
OF NEW YORK.

In considering pathological conditions in the thymus gland, especially hypertrophy, we encounter difficulties from the very outset. There is no general agreement as to its normal size during the first few months or years of life, as to the period when atrophy begins, and as to whether growth of the thymus normally takes place during the first years of life.

The weight during the first two years is variously given as anywhere between 5 and 30 grams, and unless due attention is paid to the manner in which these figures have been reached, one is likely to be drawn into grave error. During illness the gland atrophies rapidly, probably to a far greater degree than any other structure in the body. Those who have obtained their statistics of the weight from successive autopsies, which include those after prolonged and wasting disease, undoubtedly give figures very much below the normal of health. If, on the other hand, a selection is made, as was done by Friedleben, and only those glands utilized to determine the normal from healthy, well-nourished children who have suffered sudden, non-traumatic death, an equally erroneous conclusion is reached, for in this way are undoubtedly included many glands pathological in size. Friedleben's statistics have been generously made use of, and usually no attention paid to or mention made of his method of selection. Nor can the glands of children dying of fulminating infectious disease of only a few hours' duration be utilized, since

[1] By invitation.

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in many of them a pathological enlargement is present, and they are believed to have died thus rapidly in consequence of the diminished resistance which appears to accompany thymic enlargement. Statistics are not available in sufficient numbers from autopsies upon infants and young children who have met violent deaths to determine the normal. Until they are, exactness is impossible. It seems likely that 15 grams represents approximately the average weight throughout the first two years of life, and yet I believe that even among apparently normal individuals there is a great variation in size, and that glands weighing considerably more than 15 grams are not very unusual. Indeed, it seems probable that the pathological complex known as status lymphaticus is very much more common than is usually supposed, and may, after persisting for a number of years, eventually disappear. The evidence that supports this view is, first, the decided number of older children and young adults that present this condition after death from contagious disease.

Daut found, in 79 cases dying from diphtheria, 23 examples of status lymphaticus; Elser, in the 1904 and 1905 epidemic of cerebrospinal meningitis, in New York, found 6 examples of status lymphaticus in 23 autopsies, and Norris, 15 examples in 39 autopsies. All of the acute fulminating cases were in patients of this habitus. It seems only rational to suppose that without such infection these individuals might have lived years, and it certainly seems irrational to suppose that all individuals with status lymphaticus become infected and die. Further evidence is afforded by Hochsinger's painstaking observations on the size of the thymus in living children, which he made by means of percussion and radiograms.

Almost all the children examined were under a year of age, but of 29 apparently perfectly normal infants, he found in 7 the thymus to be large both by percussion and by radiogram, and to show the broad shadow above the heart which is characteristic of the enlarged thymus. Furthermore, children who have met accidental deaths from serious injury have shown glands oftentimes larger and heavier than those in reported cases of thymus death. With these points in mind, and with the knowledge that as a result of illness the thymus atrophies rapidly and progressively, a certain amount of skepticism has arisen in regard to the condition of status lymphaticus. This has been

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expressed by Richter, based upon his experience in medicolegal autopsies. He believes the so-called status lymphaticus to be very common in strong, young people, and in healthy children to be, perhaps, the regular finding. The majority of authors with post-mortem experience do not, however, subscribe to his statement that in cases of sudden death in infants, anatomical lesions sufficient to account for this are usually to be found. Richter's contention in regard to small children would be exceedingly difficult to meet did not older children and young adults exhibit the same pathological picture which in them we know to be decidedly abnormal, and we know this as a result of autopsies on a sufficient number of accidental deaths which establish the normal, Richter to the contrary notwithstanding.

In spite of the realization that the thymus varies much in size, there has been a general unanimity in the acceptance of Paltauf's views in regard to status lymphaticus as a pathological entity. Before, however, relying at autopsy upon this condition as the explanation of death, the most painstaking and careful examination of all organs should be practised, and at times bacteriological examination is necessary. Norris, in the statistics previously quoted, found status lymphaticus associated with several cases of cerebrospinal meningitis of the fulminating type, in which death had occurred so rapidly that there was only hyperemia of the meninges of the brain and no exudate whatever. Cultures alone allowed of a diagnosis, and the presence of an epidemic alone excited suspicion.

We usually see the condition of status lymphaticus in children under eighteen months of age. They are generally well nourished and may be somewhat rachitic. I have seen an enlarged thymus in but one malnourished child. The enlarged thymus gland is the striking feature, though it may not be larger than some authors consider normal, as Beneke and Biedert have with justice pointed out. The gland may be so increased in size as to reach far into the neck and so low as to almost cover the anterior surface of the heart. The weight is increased to as much as 50 grams in certain instances, and in adults weights of 150 grams have been reported. Upon the posterior aspect of the gland may be found grooves corresponding to the structures behind it. When autopsy has been delayed, areas of softening are found

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throughout the thymus, and this softening is said to take place more rapidly in large than in small glands. Upon cut section may appear the enlarged or cystic Hassell's corpuscles. There is usually a marked hypertrophy of all the lymphoid structures of the body. The tonsils and adenoids are large and the lingual follicles increased in size. The cervical, bronchial and mediastinal lymph nodes are somewhat enlarged, and especially striking is the increase in size of the mesenteric nodes. Peyer's patches and the solitary follicles of the intestine participate in the process, especially those of the large intestine. The spleen is usually greatly enlarged and the Malpighian follicles are very striking on the cut surface, increased to two or three times their normal size. The enlargement of the thymus is practically constant, and that of the lymphoid structures usual but not invariable.

There are often small hemorrhages into the serous membranes of the thoracic cavity, and at times a little pulmonary atelectasis.

Microscopically the changes in the thymus are chiefly those of hyperplasia. The corpuscles of Hassell are at times increased in size and number. Eosinophile cells of the mono- and polynuclear variety are very numerous, more so than in the normal glands of young children. A few myelocytes and giant cells resembling those found in bone marrow are also present. In general, the structure is normal.

The changes in the lymph nodes and lymphatic structures of the tonsils, spleen, and intestines consist of a hyperplasia and a proliferation accompanied by degeneration of the cells of the germinal centres. This proliferation is frequently endothelial in type, such as is to be seen in various infectious processes and especially in diphtheria.

This change is looked upon by some as a lymphatic exhaustion rather than as a hyperplasia.

There has been much discussion in regard to the evidences of compression at autopsy. There are on record a few, but a very few instances, with undoubted postmortem evidences of tracheal compression. The cases of Lange, Barach, Grawitz, Clessin, Beneke, Jessen, Flügge, and Strassmann, belong to this class. The great majority of pathologists, however, have failed to observe this. Friedleben, Paltauf, and Richter expressly state that they have never seen it. Paltauf says that it is easy to be led into error and think that there is

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tracheal flattening if the head is drawn sharply backward, but that the flattening is caused from behind by the prominent vertebræ. Occasionally he noticed a slight furrow on the right side of the trachea anteriorly, just where this entered the chest, which was caused by the right carotid. It has been recently urged that a proper opinion can only be reached if the dissection is made from the neck down and the trachea split from above before the sternum is removed. This is exactly the method employed by Paltauf, always with negative results. Bovaird used this method at the New York Foundling Hospital for many years, and never saw evidence of compression. During the last seven years, at the same hospital, my experience has been similar. Acute dilatation of both sides of the heart has been reported by Lange. In the very great majority of cases, reported by the most competent observers, autopsy has failed to reveal evidences of compression sufficient in any way to account for death.

There have been many different opinions in regard to the cause of death, and there is a sharp line separating those who think the death a mechanical one due to pressure and those who believe that such a death is rarely, if ever, possible.

Of the pressure theories, the one that merits the first consideration is that of tracheal compression, because it has had the most adherents and because it seems the most plausible. The recent champion of this theory, Warthin, writes, in Osler's *System* "The chief symptoms of thymic enlargement are those of tracheal stenosis." "All the symptoms and all the operative and postmortem evidence point to a suffocation resulting from tracheal stenosis and secondary laryngeal spasm as the chief, if not the only cause of the fatal termination."

It must be admitted that there are instances reported in which the thymus has undoubtedly exerted pressure upon the trachea with severe resultant dyspnea, and that the dyspnea has been promptly and permanently relieved by operative interference. Such are the cases of Siegel and Rehn, von Purrucker, König, and Ehrhardt. The clinical course of these cases, however, was very different from that of the ordinary status lymphaticus. Siegel's and Rehn's case had had severe and increasing dyspnea for four weeks, both of König's cases had been dyspneic for weeks, the dyspnea in Ehrhardt's case

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had lasted three months, and that in the child operated on by von Purrucker for two and one-half years.

With the exception of a very small percentage of cases, anatomical evidence of compression is lacking, as has been seen, at autopsy. To meet this lack it is claimed that the congestion or edema of the thymus chiefly responsible for the pressure disappears after death. This contention makes necessary the employment of clinical proof in opposition. In the great majority of instances the victims of status lymphaticus die suddenly in a few seconds or in the course of a few hours. Theoretically it is impossible to conceive that a congested or edematous thymus could exert sufficient pressure to cause immediate death in an individual who up to the very time of his decease had shown absolutely no symptoms of dyspnea whatever, and positively conclusive is the testimony of Pott and Escherich. Pott saw four children die while he was depressing their tongues with a spatula. There was cyanosis, gasping respiration, and convulsive movements, but he noticed in every instance that the heart had ceased beating when he examined it, and that attempts at respiration were continued for a time. In asphyxia, the heart always continues to beat after the cessation of respiration. Escherich had a similar experience.

There are lacking also the great and persistent cyanosis and edema of the head, neck, and upper extremities which one would expect from pressure upon the innominate veins immediately behind the thymus, and whose walls are so much softer and less resistant than the firm trachea. The thymus is a soft, pliable organ, and would grow in the direction of least resistance away from the position in which it would be subjected to pressure. That it is grooved on its posterior surface by the soft structures with which it lies in contact makes it still more improbable that it could affect the resistant trachea. The great mass of the thymus, moreover, is not behind the upper aperture of the chest in the "critical space" of Grawitz, but well below this, where there is ample room for it to spread downward and to the sides. Satisfactory evidence of tracheal stenosis is also lacking clinically and pathologically in those children dying after a lapse of several hours. The same arguments used above hold, but the delayed course allows of a better observation of symptoms. Dyspnea is present,

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it is true, but it is a rapid, panting dyspnea, whereas the dyspnea of true stenosis, as may be observed in laryngeal diphtheria, is comparatively slow. The lungs, too, are well aërated, and costal, epigastric, suprasternal, and supraclavicular retraction are not marked. One could not expect this with mechanical obstruction. The hyperthermia, sometimes as high as 109° F., is not accounted for by tracheal stenosis. Finally, the dyspnea and the cyanosis that may accompany it appear and disappear with great rapidity, and death may take place without a trace of either. Those who have followed the clinical course of such cases, and among them are to be included clinicians of the first rank, deny that the symptoms of tracheal obstruction have been present.

The attempts to explain the fatal outcome by pressure upon the vessels, nerves, lungs, and heart are hypotheses without anatomical or clinical evidence to support them. The case reported by Lange with cardiac dilatation is the only one that merits serious consideration. Reflex cardiac inhibition from pressure is as improbable as it is impossible to disprove.

With the discarding of pressure as more than a very infrequent factor, nothing remains to explain death but the pathological complex of enlarged thymus and lymphatic structures known as status lymphaticus. It has been urged with some reason that this complex is of a very heterogeneous nature; that the integral parts making up the whole may arise as the result of widely different causes, and that the whole is, therefore, a fortuitous combination.

On the other hand, there have been enough instances of this condition, in the experience of every pathologist, to bring about almost complete unanimity of opinion that there is such a pathological entity as status lymphaticus, and that those exhibiting this condition are especially liable to sudden death, and exhibit in general a diminished resistance to physical and bacterial insult. More than this Paltauf did not claim. With marked conservatism he pointed out the physical characteristics of these individuals and the association of lymphatic and thymus hyperplasia, leaving as entirely undetermined the method of the production of cardiac syncope to which he ascribed death.

Losing sight of the moderation of Paltauf's attitude and his thorough understanding that the determining cause was still to be sought, it has become customary to speak of status lymphaticus as if it were an

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entirely plain condition and perfectly sufficient to account for death. It must be well understood that when we say status lymphaticus we only mention the physical type of the individual that is liable to succumb, the form of beaker in which the mysterious reaction takes place. With so indefinite and inadequate an explanation we cannot rest satisfied.

Soehla's experiments have often been quoted as pointing toward a possible explanation of the cardiac syncope. He injected animals intravenously with the aqueous extracts of thymus glands, with a resultant fall in blood pressure and cardiac acceleration. He also claimed an increased effect when an hypertrophied thymus was used. Swale Vincent repeated these experiments, and was able to confirm the depressor effect; but showed, further, that all methods of extraction yielded depressor substances whose effects were comparable in all respects to those obtained by the injection of extracts from any animal tissue. That accordingly only very pronounced effects could be regarded as specific, and these were lacking.

To investigate the assumed toxicity of the thymus in a different way, Dr. A. N. Richards and I ground up to a powder, after freezing with liquid air, the large thymus from a case of sudden death. Fifteen grams of the powder were suspended in salt solution and injected into the peritoneal cavity of two kittens. Had the thymus contained toxic substances, so powerful as to cause sudden death in a child, the effect of this should have been prompt in appearance, but there was none noticed.

Hyperthymization of the blood, that is, the presence in excess in the circulation of the hypothetical internal secretion of the thymus, has been suggested as the cause of death. Dr. Richards and I injected into the peritoneal cavity of a kitten, on each of two occasions, 75 c.c. of blood obtained aseptically at autopsy from two cases of status lymphaticus. No symptoms, whatever, were noticed and the kitten was kept under observation for many weeks.

Blumer's suggestion that subjects with status lymphaticus are born with an instability of the mechanism regulating the "horror autotoxicus," and that they are subject to intermittent attacks of lymphotoxemia which may be sufficient to cause death by cardiac paralysis is a suggestion only.

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In the absence of assured toxicity of the blood and thymus, it becomes pertinent to ask if the hypertrophy may not be the result of the failure of some tissue or organ to properly play its part in the economy, and may not, therefore, be regarded as an attempt at compensation. Warthin has expressed himself as believing that the lesions in the spleen, lymph nodes, and marrow are essentially those of lymphoid exhaustion, and that the thymus hypertrophies to compensate for this exhaustion. No reason is assigned for the exhaustion, and if the thymus is composed of lymphoid tissue it is difficult to see why it should not also undergo the exhaustion which the other tissues suffer. It was difficult enough to find a satisfactory explanation for the hypertrophy when the thymus was believed to embrace lymphoid tissue. The subject has been further complicated by the recent evidence which goes to prove the dissimilarity in structure between the thymus and lymph nodes. The thymus is epithelial in origin, but has been supposed to undergo transformation into a lymphatic structure.

Hammer and Stöhr have recently brought forward strong evidence to prove that the thymus is epithelial in its structure and always remains so. Stöhr, whose opinion commands universal consideration, says that "Neither in its entirety nor in any single particular, is a comparison of the thymus with a lymph node possible. They are entirely different organs." There are biological and chemical characteristics which also point toward a decided difference in structure.

Bang found the amount of nucleo proteid (that substance so characteristic of the nuclei of true glands), to be in the thymus at least five times that present in the lymph glands, which speaks for a difference between the cells of the two structures. The fact that thymus glands undergo softening with resulting cystic areas, the so-called thymic abscesses, is evidence of the presence of a proteolytic enzyme which lymph glands do not contain.

Finally, it is impossible by injections of thymus glands to produce lymphocytotoxins, as was done with lymph nodes, bone marrow, and spleen by Flexner and Bunting.

I tried in vain to do this four years ago, and Moorhead was also unsuccessful. Did the thymus contain lymphoid tissue there is every reason to suppose that lymphocytotoxins would be formed. These

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embryological, histological, chemical, and biological facts constitute strong proof of the non-identity in structure of thymus and lymph nodes. If further study substantiates this, the thymic hypertrophy cannot be looked upon as compensatory for any change in the lymphatic apparatus. If it is compensatory, it is for some other organ at present unknown.

The suddenness of the cardiac syncope without discoverable cause and the immediate fatal effect produced by cold bathing and such slight traumatism as depression of the tongue, injection of antitoxin, and the like, point strongly toward the phenomenon as being of nervous origin, but there is no explanation for this to be found in the most careful examination of the brain, cord, or nerves.

Twenty years after the annunciation of Paltauf's views we find ourselves still without a satisfactory explanation for death in status lymphaticus.

The sifting of evidence in regard to an obscure subject and the discarding of vague theories that befog it at times enable us to get a clearer perception of where we stand. It is this sifting and this discarding that I have attempted to do. *February* 25, 1909.

Tumor Growth in Childhood.

By DAVID RIESMAN, M.D.

It is impossible to give figures that will express the comparative frequency of tumors in childhood and in adult life. Few statistics of a general character are available, those to be found dealing either with tumors of special types, such as the malignant growths, or with those of special organs. To the first class belong the statistics of W. Roger Williams,[1] who found among 942 malignant tumors 25 in persons under twenty, while Isaia,[2] among 167 sarcomas in all ages, found 11, or 6.5 per cent., in children under sixteen. To the second class belong the statistics of Albarran, quoted by Steffen,[3] who, among 252

[1] Lancet, May 1, 1899.
[2] Il Policlinico, 1904, xi; sez. chir., pp. 67, 160, 237.
[3] Die malignen Geschwülste im Kindesalter.

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cases of tumor of the bladder, found 9 in persons under the age of twenty. Frisch,[1] among 390 tumors of the bladder, found 3 in childhood. Pepper,[2] in 46 cases of primary sarcoma of the suprarenal body, found 11 in children ranging in age from nine months to ten years, while 13 of Ramsay's[3] 51 cases of sarcoma and carcinoma of the suprarenal gland occurred in early life. Epithelial growths are decidedly less common in children than those derived from the connective tissues. This is especially true with regard to the malignant tumors, for the sarcoma is far more frequent than the carcinoma. The principal sites of malignant tumors in children are the kidney, the brain, the intestines, the ovaries, and the skin, which occupy a far lower place in the scale of frequency in adult life. As a rule, malignant tumors exhibit a more rapid growth in childhood than do the corresponding tumors in adult life.

Taking up the tumors seriatim, I shall begin with the *fibromas*, tumors of the type of fibrous connective tissue which have been found in the skin, the bladder, the breast, the trachea, and elsewhere. Concetti,[4] in 42 cases of tumor of the bladder, found 7 fibromas. A tumor of the trachea is reported by Elsberg.[5] *Lipoma*, a tumor composed of fatty tissue, is not a common growth in children. It may occur in the skin as a single or multiple tumor, and has been found in the breast.[6] *Chondroma* as a pure cartilaginous growth is very rare, but as a constitutent of other tumors, chiefly the so-called mixed tumors of the salivary glands, the ovary, and the testicle, it is common. Chondroma of the patella is described by Ray.[7] Bony tumors, *osteomas*, are also rare; cases have been reported by Frauenthal[8] and Sevestre.[9] *Angioma*, or hemangioma, is a frequent growth in childhood, and is nearly always congenital. Parker, quoted by Comby,[10] among 558 nevi, found 500 in children under one year of age, while Porta,[11] among 151, found 55 present at birth, 32 had developed

[1] Wien. klin. Woch., 1907, xx, 1205.
[2] Amer. Jour. Med. Sciences, March, 1901.
[3] Johns Hopkins Hospital Bulletin, 1899, x, 24.
[4] Arch. de méd. des enfants, mars, 1900.
[5] Medical Record, December 1, 1906.
[6] Jopson, Speese, and White, Annals of Surgery, November, 1908.
[7] Lancet, 1905, i, 159.
[8] Arch. of Pediatrics, 1907, 710.
[9] Bull. de la Soc. de péd., June, 1906.
[10] Traité des mal. de l'enfance, v, 810.
[11] Ibid.

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in the first year, 44 between the first and fourteenth, and 10 after the fourteenth year.[1] For unknown reasons angioma is commoner in girls than in boys. Angiomas have usually been ascribed to obstetric trauma, though Virchow attributed them to trauma during pregnancy. There are two varieties—the simple angioma, most common in the skin, and the cavernous angioma, or cavernoma, found in the mucous membranes and internal organs. Angioma of the nervous system is reported by Finkelnberg.[2] *Chylangioma* is also found in childhood, one of the mesentery being reported by Tugendreich.[3] *Myoma* is rare in childhood. *Rhabdomyoma* has been, found in the heart[4] and in the testicle and kidney; in the latter organs, however, nearly always in association with other tumor elements. The non-striped variety of muscle tumor, the *liomyoma*, is extremely rare in childhood. Concetti[5] has collected 6 cases of liomyoma of the bladder. *Neuroma* is comparatively frequent, the favorite site being the region of the eye. It usually takes the form of the plexiform neuroma, which in look and feel suggests a collection of earth worms under the skin, and has a slow but progressive growth. Neurofibromatosis, a condition characterized by the formation of tumors, usually fibromas, along the course of the nerve trunks, is met with in children.[6] A ganglionar neuroma is reported by Glinski.[7]

Sarcoma is by far the most common tumor of childhood. It may be of any of the histologic varieties, though the giant cell and the melanotic sarcoma are rare. The sites in the main are the same as in adult life. The 11 cases collected by Isaia[8] were distributed as follows: 5 in the jaw, 1 in the antrum of Highmore, 1 each in the sternum, tibia, and dura, and 2 in the eye. Sarcoma is frequent in the brain, Starr[9] having found it 34 times among 147 true brain tumors. If to these are added the gliosarcoma, then sarcoma becomes the most frequent of brain tumors, the tyroma, or tubercu-

[1] Another large collection of hemangiomas (125) is published by Graff, Zeit. f. Kinderheilk., xxviii, 162.

[2] Deutsch. Zeit. f. Nervenheilk, xxix, No. 1.

[3] Arch. f. Kinderheilk., 1906, xliv, 21.

[4] Knox, Arch. of Pediatrics, 1906, p. 561.

[5] Loc. cit.

[6] Weber, Monats. f. Kinderheilk., 1906, v, 192.

[7] Monats. f. Kinderheilk., 1908, v, 702.

[8] Loc. cit.

[9] Keating's Cyclopedia, iv, 551.

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lous tumor, being naturally excluded from the list of true tumors. In the internal organs, aside from the brain, sarcoma is rare. When found it is frequently a congenital growth. Pepper[1] reports a case of congenital sarcoma of the liver and suprarenal gland and collects five others from the literature. The disease was probably primary in the liver and metastatic in the suprarenal. Five of the six occurred in female children; in one the sex was not mentioned. A striking feature pathologically was the infiltrating character of the growth of the liver, and the hemorrhagic nature of that of the suprarenal body. Pepper, as already mentioned, has collated from the literature eleven primary sarcomas of the suprarenal gland in children. Tileston and Wolbach[2] have described as a clinical entity a peculiar primary sarcoma of the suprarenal gland which is associated with sarcoma of the cranium. The symptom that usually first attracts attention is exophthalmos. Ramsay,[3] among 26 cases of suprarenal sarcoma, found 8 between the ages of six months and ten years. Sarcomas of the kidney are quite common in the literature, but it is more than likely that a large proportion of these really belong to the class of mixed tumors to be described below. Shannon,[4] Rush,[5] and Jones,[6] are among those that have reported true cases of renal sarcoma. A considerable series of cases of sarcoma of the bladder (23 among 32 bladder tumors) has been collected by Steffen.[7] Sarcoma of the prostate in children is mentioned in the monograph of Steffen and in the thesis of Fraenkel.[8] Sarcoma of the vagina is relatively frequent,[9] though many reported under the name of sarcoma were probably mixed tumors. The same thing is true of sarcoma of the testicle, though some tumors of this organ are endotheliomas, and therefore belong to the sarcomas. There is a widespread belief that the undescended testis is especially predisposed to sarcomatous change, but the evidence in favor of this is, according

[1] Loc cit.
[2] Amer. Jour. Med. Sciences, June 1908.
[3] Johns Hopkins Hospital Bulletin, 1898, x, 24.
[4] Arch. of Pediatrics, 1907, p. 922.
[5] Ibid., April, 1906, p. 857.
[6] Ibid., April, 1906.
[7] Inaug. Diss., Leipsic, 1906.
[8] Die malignen Geschwülste im Kindesalter.
[9] Rollin, Rev. de gynécol., 1906, x, 3.

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to Riesel[1] and Oberndorfer,[2] not convincing. Sarcoma of the uterus has been reported by Lorlhioir.[3] With regard to the alimentary canal, sarcoma has been found in the stomach,[4] in the intestine,[5] in the appendix,[6] in the liver,[7] and in the pancreas.[8] Other sites of sarcoma are the eye and the orbit,[9] the skin,[10] and the bones.[11] Sarcoma also occurs in the lymphatic glands, though many reported under that name are not sarcomas, but hyperplasias of a different nature. This criticism, however, does not apply to sarcoma of the retroperitoneal glands.

Under the head of sarcoma I shall also consider the *chloroma*. This is a greenish colored tumor occurring in the temporal and parietal regions of the skull, the hard palate, the sternum and ribs, rarely in the skin. It is almost confined to children under the age of fifteen years, and is vastly more frequent in the male than in the female sex—36 to 10.[12] The course is acute (four to six months) and the most striking symptom is exophthalmos, as it is also in the condition described by Tileston and Wolbach.[13] Histologically, two types of chloroma may be distinguished, one in which the cells are large and lymphocytic, similar to those found in acute lymphatic leukemia; and one in which the cells resemble the myelocytes. These features have led Dock,[14] Warthin,[15] and others to the view that chloroma is really a form of leukemia and not a tumor in the strict sense. The nature of the green color from which the tumor takes its name has not been

[1] Arbeiten a. d. pathol. Institut Leipzig, 1903, Heft ii.

[2] Lubarsch and Ostertag, Ergebnisse, Jahrg. II, 1908, i, 1156.

[3] Jour. de Chir., August and September, 1901.

[4] Finlayson, British Medical Journal, December 2, 1899.

[5] Siegel, Berl. klin. Woch., August 28, 1899.

[6] Harte, Annals of Surgery, June, 1908.

[7] Pepper, loc. cit.

[8] L'Huillier, Virchow's Archiv, 1904, clxxviii, 507; and Litten, Malherbe, and Piccoli, quoted by L'Huillier.

[9] Davis, The Post-Graduate, December, 1899; Ring, New York Medical Journal, 1905, p. 159.

[10] Junge, Inaug. Diss., Kiel, 1906; Fabry, Verh. d. deut. derm. Gesellsch., 1906, x, 350. Beunnan, Bull. Soc. derm. et syph., 1906, p. 251.

[11] Graham, Arch. of Pediatrics, 1907, p. 788; Venot, Jour. de méd. de Bord., 1909, xxvi, 542.

[12] Benjamin and Sluka, Jahrb. f. Kinderheilk., 1907, 65, Ergänzungsh., 87.

[13] Loc. cit.

[14] Amer. Jour. Med. Sciences, August, 1893, 152.

[15] Trans. Assoc. Amer. Phys., 1904.

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definitely determined, but it is supposed to be due to the compactness of the highly granular cells.

Hypernephroma is a tumor drived from misplaced adrenal tissue. It is found primarily in the kidney, and histologically closely resembles the medullary substance of the suprarenal gland. It has a tendency to give metastasis to the bones.

An important and common new growth in childhood to be taken up at this point is the so-called *mixed tumor*, which passes under many names in the literature, such as sarcoma, carcinoma, myxosarcoma, rhabdomyoma, adenosarcoma, etc. It is found chiefly in early life. Paul[1] observed one in a newborn infant. The statistics of Heineke[2] showed 11.1 per cent. in the first year, 21.5 per cent. in the second and in the third, 12.6 per cent. in the fourth, 14.8 per cent. in the fifth, 6.7 per cent. in the sixth, 3.7 per cent. in the seventh, 4.4 per cent. in the eighth, 1.5 per cent. in the ninth. The principal seats are the kidney, the ovary, and the testicle. The growth of the tumor is rapid in contradistinction to that of hypernephroma, which is slow. Metastasis is not common, occurring in about 30 per cent. of the cases, chiefly to the lungs and liver. A curious feature of the tumors is that they do not directly involve the substance of the organ in which they are found, but press it aside. This is particularly noteworthy in the kidney. The surface of the section may be soft or gelatinous; at times it shows lobulation. Necrosis and hemorrhagic softening are common. The histologic structure is complex; striped and smooth muscle tissue, cartilage, adipose, mucoid, and elastic tissue, as well as glandular elements are found. In a rare case, reported by Muus,[3] epidermal elements in the form of pearly bodies were present. The complexity of the tumors has given rise to a number of opinions as to their origin. Without going deeply into the subject it may be stated that the most acceptable view is that they are derived from a misplaced blastomere.[4]

[1] Quoted by Wilms, Die Misch-Geschwülste, 89.

[2] Maligne Geschwülste der Niere im Kindesalter, Inaug. Diss., München, 1897.

[3] Virch. Arch., 1899, Band clv, p. 92.

[4] Those who are interested are referred to Wilms (loc cit.); Bonnet (Monatsschr. f. Geburtsh. u. Gynäk. 1901, xiii, S. 149); Marchand (Missbildungen. Ref. in Eulenburg's Realenzyklopädie, III. Aufl. Band xv); Oberndorfer (Lubarsch and Ostertag, Ergebnisse, Jahrg. IX, 1908, i, 1156); Schneider (Jahrb. f. Kinderheilk, 431); Hedren (Ziegler's Beit. xl, Heft ii); Monti (Kinderkrankh. in Einzeldarstell., 1903); Brindeau and Glorghin (Bull. méd. 1897, 417); Kelly (Surgical Diseases of Children, 1909).

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A peculiar mixed tumor occurs in the vagina, which the Germans call *traubiges Sarkom*, and which macroscopically presents itself as a soft villous tumor and is locally destructive. It may perforate into the bladder. Histologically it is composed of round and spindle-shaped cells, and striped and non-striped muscle tissue.

Glioma, a tumor derived from the neuroglia of the nervous system, is common in childhood, and in the brain is nearly as frequent as sarcoma. It also occurs in the retina.[1]

The most common benign epithelial tumor in childhood is the *papilloma*, which is found in various mucous membranes, but is particularly common in the larynx. About one-fourth according to Monti[2] are congenital. Some arise on the basis of a chronic laryngitis or a tracheotomy, hence are doubtfully classed as neoplasms. Among the more recent articles on papilloma of the larynx are those by McGreery,[3] Patterson,[4] Neubauer,[5] and Clark.[6]

Adenoma and other benign epithelial tumors appear to be rare in childhood. Tumors and enlargements of the thyroid gland (struma) are fairly common.[7]

Carcinoma is often mentioned in the literature dealing with tumors in childhood, but many of the reports date back to a time when an accurate differentiation between sarcoma and carcinoma was not yet made. To show the unreliability of the older observations I need only state that of 390 so-called carcinomas of childhood collected by Phillipps[8] only 37 stood the test of criticism.

Cancer is about equally frequent in both sexes in childhood, due to the fact that cancer of the breast and uterus so common in women is almost never found in girls. Carcinoma is rare below the seventh year; increases up to the tenth; reaches its height at the twelfth; declines to the fourteenth; and remains about the same level to the fifteenth. The relative rarity of carcinoma as compared with sarcoma

[1] Arch. de méd. des enfants, 1906, ix, 615.
[2] Kinderkrank. in Einzeldarstell., iii, 192.
[3] Medical Record, July 14, 1906.
[4] Lancet, July 21, 1906.
[5] Jahrb. f. Kinderheilk., lxi, 21.
[6] Boston Medical and Surgical Journal, 1905, ii, 377.
[7] Karl Fischer, Beit. z. klin. Chir., 1907, liv, 161, a case in a new born child; Herb, Amer. Jour. Med. Sci., June, 1906, a case of teratoma.
[8] Zeit. f. Krebsforschung, 1907, v.

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is indicated in the statistics of Roger Williams,[1] who among 806 found only one under twenty, and among 136 sarcomas, 24 under twenty. The organs most frequently affected by juvenile cancer are the intestines, ovaries, and skin. The stomach may be a seat of cancer in early life,[2] also the liver.[3] A surprisingly large number of the cases of carcinoma of the appendix in early life have been reported—(Harte,[4] Zaajer,[5] Baldauf,[6] Battle,[7] and others).[8]

Cysts, including the ecchinococcus cyst, occur in children and require no special discussion. The teratoma, as might naturally be expected, is a common juvenile tumor. Two varieties are described, the solid and the cystic (embryoma). To the teratoid tumors belong the mixed tumors already described, as well as dermoid cysts and highly complicated growths due to developmental errors.

In this brief survey of tumors in childhood I have not attempted to give a complete review of the subject, but have cited, here and there where necessary or appropriate, cases from the more recent literature. *February* 25, 1909.

Neuropathology in Childhood, with a Consideration of Pathological Factors in Some Cases of Retarded Mental Development.

By D. J. McCARTHY, M.D.

NEUROPATHOLOGY in childhood does not differ essentially from that of adult life. We may find that the same pathological processes and the results of such processes upon the structure of the nervous system are approximately the same. The results, however, so far

[1] Loc. cit.

[2] Osler and McCrea, New York Medical Journal, April 11, 1900, lxx, 581; 759.

[3] Plaut, Arch. f. Kinderheilk, 1908, xliii, 249; Petrone, La Pediatria, March, 1907, No. 3, abstracted in Jahrb. f. Kinderheilk., lxvii, 369, adenocarcinoma of the liver in an infant four months old.

[4] Annals of Surgery, 1908, xlviii, 968.

[5] Beit. z. klin. Chir., 1907, liv, 204.

[6] Albany Medical Annals, 1905, xxvi, 804.

[7] Lancet, 1905, ii, 291.

[8] Other references to carcinoma in early life are: Grulee, Surgery, Gynecology, and Obstetrics, 1906, 678, carcinoma of the rectum in a girl of six; Czerny, Münch. med. Woch., 1896, 241, of the rectum in a boy of thirteen; Prissmann, Dermat. Zentralbl., ix, 356, of the skin; Hall, Lancet, 1905, i, 859, of the bronchus.

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as temporary and permanent disturbance of function are concerned, are somewhat different. This is due in part to the incomplete development both of structure and function of the infantile nervous system. The central nervous system of the newborn child is only partially complete, and relatively few of the fiber tracts have received their full myelinization. Comparatively few of the higher and more fully developed functions of the brain and spinal cord are active at birth. The pathological processes which cause relatively minor disturbance in the fully formed adult brain may cause a serious and permanent disturbance or perversion of function when they occur in infancy.

Our knowledge of the various pathological processes is fairly complete. We have a fair, if incomplete, knowledge of the anatomy of the nervous system. Our knowledge of the physiology of the nervous system, on the other hand, is not only incomplete, but really not sufficient for a good working basis. This is true not only of the action of the nervous system, but is also true of its interdependent action with the other visceral functions. We have gradually come to understand that not only is the growth, development, nutrition, and metabolism of the body dependent upon the nervous system, but that, on the other hand, the development and nutrition of the central nervous system is dependent upon other visceral activity. This has led to a slightly different viewpoint. In the study of neuropathology, even the simpler forms of organic disease of the nervous system require for their elucidation a careful study of the pathological processes and visceral activity elsewhere in the economy. In the report of a case, the study of the nervous system alone is now considered of relatively little value. This must of necessity be the case not only on account of the close relationship of the nervous system to other visceral activity, but because the nervous tissues are exceptionally sensitive in their reaction to infectious and toxic processes. A serious functional disturbance of the nervous system may occur, with relatively little evidence even by the best histological methods, in the nerve cells. In order to have some clear understanding of such conditions as occur in adult life, it is necessary to study similar processes in the nervous system in infancy and childhood. While this is true in a general sense, it is more particularly so with the wide

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group of diseases either of primary deficiency of nervous function, or of an abiotic nature (*i. e.*, of an inherent lack of growth power). Among this group may be mentioned muscular dystrophies, periodic paralysis, epilepsy, Huntingdon's chorea, dementia precox, retarded mental development, and some other forms of mental instability.

I have selected for this study the subject of retarded mental development because it presents a varying histological and pathological picture. The condition of the nervous tissues studied in retarded mental development may show gross pathological lesions, or a practically normal nervous system. In the latter the cells may not show, even with the most delicate methods, any variation from the normal. To understand this latter group would be a distinct advance in the appreciation of other forms of mental disturbance without an anatomical basis. Three separate lines of study have been followed in an attempt to elucidate the subject—the clinical, embryological, and pathological. While the clinical side has not been altogether barren, it has, on the other hand, given insufficient and unsatisfactory results. The clinical side has been mainly directed toward the influence of heredity. One important fact has resulted. It was at one time assumed that syphilis and alcohol in the parents were the important factors in the production of mental deficiency in the children. An accumulation of statistics of some twelve thousand cases appears to show (taking into consideration the errors and faults of massed institution records) important influence to be one of a condition of lowered nutrition mainly due to tuberculosis. Correct conclusions cannot, however, be drawn from this information until the effects of associated factors, such as that of transmitted infection, deficient blood tension during development, lowered vital tone, and the effects of the disturbance of various internal secretions on the development, are worked out. An additional clinical factor is that caused by prolonged, difficult, and instrumental delivery. It is well known to the clinician that cases of retarded and deficient mental states are most frequent in the first-born child, and more particularly so when there has been a marked prolongation of the labor period.

While direct traumatism to the children either by passage through the birth canal or as a result of instrumental delivery, has been

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most frequently considered the cause of this condition, there are other factors, which will be discussed later, which are of equal, if not major importance.

The influence of the convulsive disturbances of childhood, while closely related to these factors, does not come within the scope of this paper.

A study of the factors influencing the development of cerebral tissues, and more particularly of the cortical cells, points to a new, and for the most part unexplored field of thought. Czerny, in an experimental and pathological study of the adrenal gland in congenital hydrocephalus, found a defective development of the medulla of the adrenal. He showed that methylene blue injected into the cerebral ventricles first made its appearance in one of the vessels supplying the adrenal, and came to the conclusion that the adrenal played an important part in the development of the nervous system and more particularly in the production of internal hydrocephalus. This work has not been supported by subsequent work, neither, on the other hand, has it been disproved. It is of considerable interest, in view of the recent work on the pituitary, thyroid, adrenal, testicle, and ovary, on the growth and nutrition of the body, and of pathological lesions of these organs in some types of defective and perverted mental states. In studying the influence of toxic processes on active cells, it should be borne in mind that only when marked and irreparable damage is produced is there any evidence of it shown in the histological picture. It may be considered that the function of the cortical cells at birth is predetermined, but not established; that even temporary disturbance or perversion of function at this time may have serious results later in childhood or adult life. It is extremely difficult to study the influence of endogenous or exogenous forms of intoxication during prenatal life. A comparative study of disturbed activity of some of the above-mentioned glands, whose functions are to a certain extent interchangeable during infancy and, later, childhood and adult life, points to a distinct variation of the reaction of the nervous system at these different periods. A study of the thymus, for instance, shows as a result of disturbed function in infancy, thymic asthma, and sudden death. In later childhood, in two cases under my own observation, a persistent and enlarged thymus

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gave rise to an hallucinatory, delusional condition lasting over several days, with reflex dysphagia. In both of these cases hydrophobia was diagnosticated on account of the inability to swallow and the disturbed mental state. In adult life, a grave neuromuscular condition, myasthenia gravis, is associated with, and probably caused by, the pathological changes secondary to a persistent thymus.

Weber, in 1898, reported the influence of free blood in the neighborhood of the ganglion cells, in the production of iron infiltration. The ganglion cells in the neighborhood of the microscopic hemorrhages gave all the biochemical reactions for hemosiderin. The following year I placed on record a case of the same kind. In both cases the infiltration of the cells with this substance led to a disintegration of the cell. The further study showed it to be an intermediate stage in the process of calcification of the ganglion cell. A somewhat similar process of an intermediate grade, giving all the biochemical reactions with the microscopic test for hemosiderin, was found in the ganglion cells of the cerebellum of a rabbit which had died from rattlesnake venom with convulsions and cerebellar symptoms. There was here presented a change of function, or of functional status, from normal. That neuroglia cells act as scavengers has been demonstrated by Bevan Lewis and others. As a result of these changes of function, a sclerotic condition resulted. The ganglion cell whose future is to be one of motor and psychic activity, and where the fixed status is deranged or disturbed by a perversion of function to one of elimination of some foreign substance, and more particularly to one which has been shown to lead to a damage of function and structure of a cell, a serious result in the life history and activity is rather to be expected than otherwise. Where the same process is widespread and extensive throughout the cortical tissues, this change in the potential power will necessarily affect not only the individual cells, but the brain function as a whole. Such a condition is found in prolonged and difficult labor, with marked and persistent passive congestion. I have shown elsewhere that in continued passive congestion in adult life, not only an edematous condition, with a disturbance of nutrition of the cell, would result from interference with the general circulation, but also an advanced capillary osmosis of red blood cells obtains. In such cases gross

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venous hemorrhage is rare; but capillary microscopic leakage is not infrequent. That a similar and more extensive condition may take place in childhood is sufficiently in evidence by the microscopic and gross specimens here presented (on exhibition). When a condition of actual injury to the brain takes place as a result of venous thrombosis and gross hemorrhage, the cerebral palsies of childhood, with varying grades of idiocy, imbecility, and epileptic manifestations, result. In the minor grades of osmotic hemorrhage due to prolonged passive congestion, perversion of function of the ganglion cell results without gross lesion and with less serious objective disturbance. That simple passive congestion in itself leads to serious damage in the life history of the cell I am not prepared to state. The combination of two such important factors as prolonged interference with the cerebral circulation and the perversion of function and nutrition of the delicate ganglion cells, as a result of free blood in the tissues, could, and I think does, lead to that interference of function and potential which is manifested in later childhood in the failure to advance in mental development beyond a certain stage. There is, indeed, in some of the cases which fall into the above category, no evident loss of power, but a certain clumsiness in the more delicate movements of the extremities, with a tendency to speech disturbance (stammering, stuttering), retarded mental development, and, in some cases, criminal tendencies.

That such conditions (microscopic blood osmosis with iron infiltration) may exist, both in the pre- and postnatal states is shown in an experimental and clinical way both in the lower animals and human beings. It is not the province of this paper to report in detail these experiments, but simply to state that in certain congenital deformities in the lower animals have been found evidence of previous capillary hemorrhage in intermediate stages of iron infiltration of the nerve cells.

That either inherited or acquired weakness or pathological lesions of the vascular system would necessarily play an important part in the production of the above conditions is evident. The influence of inherited tuberculosis and other dyscrasic states, syphilis, etc., could easily act in this way by leading to obstruction or rupture of capillaries or veins from increased pressure.

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I do not wish to be understood as taking the position that all forms of defective mental states are due to this one pathological cause, but merely to point out one of the factors in a group of cases and to direct attention to a comparative method along biochemical lines of investigation of mental states. Some such method must indeed be necessary if we are to advance in our knowledge of developmental mental states. The correlation of not only the permanent but temporary visceral disturbances with minor mental and nervous conditions, and an application of physical and chemical means with our present methods of histological and pathological investigation, will be found necessary for proper understanding of many of the mental and nervous conditions of childhood and adult life.

February 25, 1909.

Card Specimens Presented March 25, 1909.

DR. H. S. WIEDER:

Congenitally Misplaced Kidney with Double Pelvis and Anomalous Blood Supply.

The condition was accidentally encountered at postmortem performed at the Philadelphia General Hospital. The left kidney was found at the brim of the pelvis, the right kidney being in its normal situation. The condition was at first thought to be an adherent ptosed kidney, but the blood supply and the length of the ureter demonstrated its congenital origin. The chief arterial supply came from the bifurcation of the aorta, though there was also a small vessel coming from the aorta higher up. The chief venous channel was a long vein which ran upward and emptied into the vena cava a considerable distance above its bifurcation.

The left ureter was very short in comparison with the right one, being of just sufficient length to reach from the bladder to the left kidney. The ureter was forked at the pelvis, so that it really formed a double pelvis at the hilum of the kidney. The left kidney was small and the right kidney showed compensatory hypertrophy. Apparently there was no disease of either kidney. In this situation the condition could easily have been mistaken clinically for an

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adherent displaced kidney, and any one trying to operate upon it would have found more than usual difficulty because of the peculiar blood supply.

DR. C. Y. WHITE:

1. *A Heart with Congenital Perforation of the Intraventricular Septum and a Patulous Foramen Ovale.*

The child from which the specimen came had shown no evidence of being a "blue baby." It died of lobar pneumonia, at the age of three years. At autopsy, the heart was found to be greatly enlarged for the age of the child; and on examination, the intraventricular septum was found to contain a perforation large enough to admit the tip of one's little finger directly below the aortic and pulmonary valves. The blood, coursing from the left ventricle to the right side, caused a saccular dilatation of the pulmonary vessel. There was also a patulous foramen ovale, but it was shielded by a fold of the endocardium, so that it seemed probable that during life the blood was prevented from going from one side to the other.

2. *A Heart Showing a Severe Grade of Inflammation.*

This specimen was from a child about eight years old. There was a recent adherent pericardium due to a fibrinous exudate; also vegetations on the mitral and aortic leaflets. The autopsy was made within five hours after death; yet the pericardium and endocardium showed a mixed infection with a large, thin bacillus, resembling morphologically the Klebs-Loeffler bacillus, and also a diplococcus with a capsule something like the pneumococcus.

DR. A. O. J. KELLY:

Portion of Gastric Carcinoma Showing Oppler-Boas Bacilli.

This microscopic preparation of a large piece (about 2 x 1 x 0.8 cm.) of a gastric carcinoma which had been obtained after lavage from J. L., aged thirty-nine years, a male patient of Dr. John B. Deaver, at the German Hospital, shows an extraordinary invasion of the necrotic tissue by numerous Oppler-Boas bacilli.

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Pure Adenoma of the Breast.

By JOHN SPEESE, M.D.

(From the Laboratory of Surgical Pathology of the University of Pennsylvania.)

PURE adenoma is one of the rarest growths encountered in the breast. Warren[1] does not mention its occurrence in his classification based on an analytical study of 758 cases, an omission which Rodman[2] in his treatise on *Diseases of the Breast* recognizes and has corrected by adding adenoma to Warren's classification, which he indorses. A report of the following case of pure adenoma, and a collection of the cases already recorded, and their study, may prove of value in adding to our knowledge of this unusual tumor of the mammary gland.

The patient, a primipara, aged twenty-one years, was delivered at term in the maternity wards of the University Hospital, in the service of Dr. Barton Cooke Hirst, who has kindly permitted me to report the case. She gave the history of a growth in the right breast which had been noticed for several years, but had not produced any symptoms. Following the birth of her child, and associated with the establishment of lactation, the tumor, which was the size of a walnut, began to enlarge rapidly. Locally it was suggestive of a benign growth, being firm and freely movable, the skin and axillary nodes being uninvolved. The sudden increase in size was regarded as a dangerous complication, requiring immediate operative interference. The growth, therefore, was excised two weeks after the birth of the child; it was found to be well encapsulated, about the size of a goose egg, and in close relationship with the breast tissue. During the operation several milk ducts were cut, and milk flowed freely from the surface. The wound was drained, on account of the discharge of milk, but healed completely in two weeks.

The tumor measured 7 cm. in diameter, was reddish yellow in color, soft in consistency, lobulated, and well circumscribed. On section, the surface was spongy, granular, and opaque in appearance,

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and the lobules were well separated from one another. Pressure caused the exudation of a whitish fluid ascertained to be milk.

A thorough study of the tissue was made, many portions of the tumor being examined after its true nature was determined. The microscopic examination, which showed great uniformity in structure, revealed a thin, well-defined fibrous capsule, which sends prolongations into the tumor mass, forming its supporting stroma. The trabecular fibers are thicker and more cellular than those of the capsule, but do not suggest, in any respect, the fibrous hypertrophy seen in the fibro-epithelial formations. The trabeculæ divide the tumor into many lobules, which vary in size from small ones containing but a few acini, to others which are quite large and prominent.

In general, the acini are circular in outline, some are irregular in shape, a few are dilated; but in all instances they are well defined and circumscribed, and do not show any evidences of malignancy. The cells lining the acini are limited by a basement membrane, and are, for the most part, cylindrical in shape. The nuclei are rather small, deeply stained, and somewhat obscured by the granulations of the protoplasm. This condition and the numerous fat droplets present, indicate the active functionating condition of the glandular tissue. The lumina of some of the acini are filled with a secretion which is granular in appearance, and contains epithelial cells and fat droplets.

A few of the acini are dilated, the lining cells having undergone compression and appear as flat cells, resembling endothelium. In these acini, as well as in several milk ducts, a homogeneous substance taking a faint eosin stain is present in small amounts.

The microscopic appearance of the tissue, therefore, confirms the view that the tumor in this case was one of the rare forms of pure adenoma. The rapid growth was directly influenced by lactation, so that with the establishment of that function an hypertrophy of the secreting tissue of the preëxisting tumor immediately took place.

Gross[3] has contributed much to the pathology of adenoma, for he has carefully described many varieties of the growth. In collecting cases of this type, one is impressed with the carelessness with which the term adenoma is used. Many tumors, recognized from their clinical descriptions, and accurately described as fibro-adenomas,

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were incorrectly diagnosticated as adenomas. This mistake was due to the fact that the term adenoma was used by many pathologists in a general sense, and indicative of the class of tumors to which we now apply the term fibro-epithelial. With the use of the latter term now generally adopted, fewer mistakes are made in the classification of benign growths of the breast.

Billroth[4] was one of the first to call attention to the presence of pure adenoma, and recorded a case occurring in a woman aged twenty-four years. She was married, but had not borne children. The tumor was situated in the right breast, was the size of a hen's egg, immobile, and required one year to obtain its size. On palpation it felt nodular, and produced moderate pain, which radiated to the arm of the same side. The cut surface of the tumor was firm, and small cavities were seen, from which a thick yellowish substance could be expressed. The microscopic examination showed a true adenoma, which is well depicted in a drawing included with the report, which illustrates the type of epithelium and the size of the acini.

Power[5] describes a tumor of five months' duration, seen in the breast of a woman who was four months pregnant. The tumor when removed was completely encapsulated, measured four inches by two and one-half inches, and was divided into two unequal lobes, the larger of which was roughly nodulated. The fresh specimen was pearly white, and resembled freshly cut mammary gland. Histologically, the growth consisted of a number of acini or tubes with lateral diverticula.

The adenoma described by Gross occurred in an unmarried girl, aged sixteen years, was situated in the upper portion of the breast, and caused no inconvenience.. On its removal, three months subsequent to its appearance, it was found to be oval and nodulated, and measured one and three-quarter inches in length by one and one-quarter inches in breadth. At the expiration of twenty-eight months there was no recurrence. The microscopic examination showed, in addition to a few ducts and acini, an immense number of closely aggregated longitudinal and transverse sections of ducts, lined with spheroidal and cuboidal epithelium, and provided with

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a common lumen. They were contained in a delicate, young connective tissue, and were, doubtless, offshoots from dilated acini.

Several authors mention cases which they have examined and found to have been pure adenoma. It is to be regretted that such reports are too meagre to permit a study of the cases from either the clinical or the pathological standpoint.

Adenomas occur in the breast as well-circumscribed tumors, which are rather soft in consistency and are nodular in outline. The overlying skin is never adherent, but the growth is in intimate relationship with the mammary tissue. A thin, fibrous investment is demonstrable, and permits the tumor to be moved freely on the pectoral fascia beneath. The cut surface is smooth or granular, pink or red in color, and usually exudes a white fluid resembling milk. Occasionally small cysts are encountered, due evidently to dilatation of the milk ducts, as described in several cases. This feature of adenoma is inconspicuous, and has no connection with that variety of tumor described as cyst adenoma. The tumor is present as a single mass, or in some cases is divided into lobules by connective-tissue septa.

Pure adenoma has a tendency to occur at an early age, most of the cases recorded appearing between the second and third decades of life. Gross describes its growth as slow, uninterrupted, and uninfluenced by lactation, pregnancy, or uterine disorders. The majority of the cases seem to conform to this description, although in the writer's case the rapid growth of the tumor and its definite relation with the function of lactation constituted one of its interesting features. Bryant[6] has made similar observations, and records the instance of a growth which enlarged during both lactation and pregnancy.

The subjective symptoms are not marked, and unless the tumor reaches a large size, or its growth is very rapid, its presence will not cause much inconvenience. When sufficiently large to form a definite tumor mass, the adenomatous growths present the appearance and cause symptoms similar to the more common fibro-epithelial type of tumor.

The differential diagnosis between pure adenomas and the other fibro-epithelial tumors, or fibro-adenomas, may be impossible, and

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does not constitute a very important factor, as the treatment of the two conditions is the same. What difference the two forms have in regard to the possibility of malignancy is rather difficult to say. Fibro-adenomas in a small percentage of cases do undergo malignant transformation. Whether certain of the cases of adenocarcinoma may have originated in a simple adenoma is impossible to state because of the few cases available for study. It seems likely, however, that malignancy is especially prone to occur in a growth which contains so much epithelium, particularly when the tendency to epithelial hyperplasia is so well marked as in the recorded cases. Rapid increase in size certainly must be regarded as a dangerous symptom, and although the enlargement was due, in the writer's case, to lactation hypertrophy of a preëxisting benign growth, such rapid growth should be regarded as a suspicious occurrence, and warrant immediate removal of the tumor.

Discussion.

Dr. H. S. Wieder: This specimen has more than usual interest for me, for, having studied it while connected with the University Laboratory, I recognized the fact that Dr. Warren's classification of breast tumors had no adenomatous division. Dr. Rodman, before going abroad in 1907, asked me to conduct a correspondence with Dr. Warren to find out why he had excluded this growth from his classification. After sending Dr. Warren a section from this tumor borrowed from the University Laboratory of Surgical Pathology, he wrote he was following Ribbert's classification, and that he saw no reason why this tumor should not be called a fibro-epithelial tumor. I admitted this, but contended that this specimen was so unlike anything he had described in his classification that it should constitute a separate division. He thought that simplicity was desirable, and as this was a rare tumor, he did not believe that the number of divisions should be increased. With due deference to his valued opinion, this specimen is very different from all the fibro-epithelial tumors he describes, and, I think, deserves a separate place in the classification.

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Dr. Greenough and Dr. Simmons to whom Dr. Warren referred the specimen for opinion, called attention to the possibility of its being an aberrant gland, but, I believe, with Dr. Speese and others who have studied it, that it is a true tumor of the breast. Dr. Speese should be congratulated for calling attention to this rare and beautiful specimen.

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March 25, 1909.

The Flagellation of Leukocytes in the Presence of Chemical Excitants and in Other Conditions.

PRELIMINARY REPORT.

BY EDWARD M. L'ENGLE, M.D.

ROSS AND MACALISTER[1] have recently reported the result of their observation of blood treated with certain chemical substances, describing the appearance of flagella on certain of the white blood cells. In their experiments the blood was treated with the following solution:

(*a*) A volume of Unna's polychrome methylene blue diluted with an equal quantity of water.

(*b*) A neutral solution containing—

4.5 per cent. sodium citrate;
1.5 per cent. sodium chloride;
0.225 per cent. atropine sulphate.

(*c*) A 5 per cent. solution of sodium bicarbonate.

Mix 1 c.c. of solution *a*, 4 c.c. of solution *b*, 0.2 c.c. of solution *c*. A portion of this mixture is then added to an equal volume of freshly

[1] British Medical Journal, January 23, 1909.

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drawn human blood, incubated at 37° C. for a half hour, then spread on a slide, a cover glass put on, and the slide examined at a temperature of 20° C., with either the $\frac{1}{6}$ or $\frac{1}{12}$ oil-immersion objective, preferably the latter. The polychrome methylene blue is used for the purpose of staining the granules of the leukocytes, thus making easier the differentiation of the different kinds of white blood corpuscles. The nucleus will not stain as long as the cell is alive.

I have repeated the experiments of Ross and Macalister, adhering to their technique, and can confirm their findings. Certain of the cells, which on account of their size and general appearance are believed to be small mononuclears, may be seen to extrude fine, hair-like projections with a terminal granule. These at first are quite short, but gradually grow longer and are apparently in quite active motion. The length finally attained may exceed twice the diameter of the cell to which they are attached. There may be one or several of the processes on a cell. Ross and Macalister report seeing as many as twenty; I have not seen more than two on any one cell. This phenomenon may not be seen in every blood smear examined, but one or two or sometimes more cells can usually be found in which this process may be followed.

The flagella are very easily distinguished from the pseudopodia, which are formed on the ameboid cells. They resemble, in a general way, the flagella seen on bacteria, except in the possession of a terminal granule.

After a varying length of time the flagella separate from the cell and swim away as independent bodies. It was not possible in any of my cases to follow the separated flagellum and determine its ultimate fate. Its change of place was very rapid and the gradual drying of the edge of the smear caused disconcerting independent movements of the blood.

In looking over some stained smears from a case of myelogenous leukemia, I saw two or three cells which showed hair-like projections, similar in every way to those seen in fresh blood chemically treated, except that they were somewhat longer in proportion to the cell than those formerly seen. The most distinct of these I have photographed. It shows a long process extending from a myelocyte. The nucleus of the cell is stained lightly, the dark rim partly around

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it being cytoplasm. It could be noticed that the projection took the same stain as the cytoplasm. At the points where the flagella come off there is a slight triangular bulging of the cytoplasm. There are two of these projections, one extending in a straight line, but showing a slight wave at one point and with a very distinct terminal granule. The other is bent back under the cell, so that only the proximal end can be seen.

The question naturally arises as to the interpretation to be put on such a picture. We have here blood which has undergone a certain amount of manipulation, which might and probably does cause partial destruction of some of the cells, with the production of abnormal appearances in outline and staining, some of which can undoubtedly be explained as artefacts. The striking resemblance of the picture shown here, however, with what can be observed in fresh blood leads me to believe that we are here not dealing with an artefact, but with flagella formation. Its occurrence in this instance without the addition to the blood of any artificial excitant raises the question as to whether this may not be a function of certain of the white blood corpuscles in normal or diseased conditions. Ross and Macalister suggest that it may be of some importance in carcinoma, as they have stimulated flagella formation in normal blood by the addition of sera from cases of carcinoma.

At the present time any theory as to the meaning of this phenomenon must be advanced with great reserve, but in view of our ignorance of the genesis of the blood cells in general, it may not be thought too fanciful to suggest that it may be concerned in the formation and multiplication of the leukocytes. *March* 25, 1909.

Card Specimens Presented April 8, 1909.

DR. ALFRED GORDON:

Microscopic Specimens of the Spinal Cord from a Case of Pernicious Anemia.

These specimens were taken from a patient, aged thirty-six years, who, four years prior to death, met with an accident that caused a profuse hemorrhage. After the hemorrhage the patient became

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exhausted and neurasthenic. Two years after the accident he began to develop spinal symptoms—sharp pain and paresthesias in the lower extremities, and difficulty in walking. The condition grew progressively worse. He was put on arsenic and iron, but did not improve. When he came under my observation his cachectic appearance strongly suggested pernicious anemia. On examination of the blood, a marked reduction of hemoglobin was found, together with other characteristic conditions indicative of pernicious anemia. Death occurred shortly afterward.

At autopsy, the heart was found to be very flabby, and there was some involvement of the apex of the right lung. The brain and medulla showed no changes, but the spinal cord presented a diffuse degeneration. The maximum of these changes in the cord was at the level of the lower cervical and upper thoracic vertebra. The changes were both old and recent, as revealed by Marchi and Weigert methods. The case was out of the ordinary in this respect: that the degeneration was more diffuse than is the case in the majority of cases showing spinal cord changes following pernicious anemia.

DR. JOSEPH SAILER:

Specimen of Triple Perforation of the Intestines in Typhoid Fever.

The patient had a moderately severe attack of typhoid fever until four days before death, when there was a sudden rise of temperature to 106°, accompanied by symptoms of profound collapse. Perforation was suspected, but the patient steadily improved and the following day seemed well. Two days before death there was a similar attack, from which she rallied promptly. In the evening of the day before death there was a third attack, and at this time there was evidence of air in the peritoneal cavity. Operation was performed. A perforated ulcer was found and sutured. The patient died shortly afterward. The specimen was removed through the operation wound. About 18 inches above the ileocecal valve there was a perforation completely plugged by a firmly adherent omentum; 8 inches lower there was a second perforation also plugged by omentum which had been partly torn loose during the removal. About 2 inches above the ileocecal valve, there was a third perforation still closed by sutures.

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The case suggests many interesting ideas in regard to typhoid fever, particularly the proper surgical and medical treatment. In the present instance, drainage of the ileum after the symptoms of the first perforation might have been beneficial. The pathological interest consists in the occurrence of three perforations, two of which had been spontaneously cured during life by adhesions. No similar case is, I believe, on record.

DR. HOWARD T. KARSNER:

Specimens of Gumma of the Heart, Hepar Lobatum, and Hyperplasia of the Spleen.

All three organs were removed from the same body at Blockley. The liver shows the lobulated condition particularly well from the under surface. The spleen has attained an enormous size, and weighs 1600 grams. The patient showed no arteriosclerosis that could be diagnosticated as definitely syphilitic, but there is a partially calcified, well encapsulated, and slightly ulcerated gumma in the left ventricular wall of the heart just below the position of the posterior leaflet of the mitral valve. The histological appearance of the heart section was not especially typical of gumma; but the fact that the man certainly had syphilis, as judged by the condition of the liver and spleen, that the calcified mass was localized to one position and did not extend around the valve, and that there was a certain amount of softening around the calcified area, all led to the belief that the gumma was old. Histologically the calcified mass could be clearly seen. Around it were some broken-down nuclei and a large mass of lymphocytic cells, running into the interspaces between the muscle fiber cells. No epithelioid cells were demonstrable, but this was believed to be due to the fact that the gumma was old, that it had gradually progressed further and further outward, and that the epithelioid cells had become involved in the necrotic process and destroyed. The arteriosclerosis accompanying the condition had the appearance of ordinary arteriosclerosis, and was not like that usually found in syphilitic cases.

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DR. E. B. KRUMBHAAR for DR. WARFIELD T. LONGCOPE:

Multiple Papillomata of the Intestine.

These four specimens were taken from a man dying after an operation for intussusception. When brought to the hospital he was badly shocked, the case having been neglected for a couple of days. He died shortly after the operation, and at autopsy this remarkable condition was found. There were ninety-one of these papillomata of the intestinal mucosa, most of them being in the duodenum and colon, varying in size from a pea to a walnut. The largest had apparently caused the intussusception by dragging on the intestinal wall. The congested specimen without tumors is the intussusceptum straightened out. A few years ago fifty cases of what was probably this condition were collected by Duhring under the name of "polyposis intestinalis." In several of his cases the tumors showed malignant change, and were in young persons. This man was twenty-five years old. A microscopic section of one of the larger papillomata of this case shows a malignant change where the papillomatous growth is found invading the muscle tissue.

The Cutaneous Reaction of Link in Typhoid Fever.

BY EDWARD H. GOODMAN, M.D.,

AND

C. CLYDE SUTTER, M.D.*

IN the *Münchener medizinische Wochenschrift*, 1908, p. 730, Link published a preliminary report on some studies in typhoid fever with the cutaneous inoculation of dead typhoid bacilli. He uses for the purpose a five to nine days' old bouillon culture which is subjected to a thirty-hour exposure at 55° C. At the end of this time the culture is examined for motile bacilli, and if any are present the culture is, of course, rejected.

* By invitation.

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After cleansing the arm thoroughly with soap and water, alcohol, and ether, an excoriation is made, and with the point of a knife dipped in the culture the dead bacilli are rubbed in. Another spot is excoriated as a means of control, but no bacilli are inoculated. The serum is allowed to dry, after which the skin abrasions are protected by a gauze bandage. The control excoriation appears somewhat irritated in six, eight, ten, to twenty-four hours, but is distinct from the positive reaction, which in a few hours shows a papular swelling of the inoculated area with mild itching but with no constitutional disturbance. The local inflammation persists for from two to four days.

Link studied fourteen cases, five of which never had typhoid and were not suffering with typhoid while under observation, so called "normal cases;" five cases were from a paratyphoid epidemic; one case was a sporadic case of paratyphoid infection, and three cases had histories of typhoid fever.

Of the five "normal cases," three showed reddening, but not a positive reaction, one had no reaction at all, and one case showed marked reddening, becoming pale after two days. Link says the diagnosis of typhoid fever could not be excluded in this case, the Widal reaction being positive (1 to 100), so it is not quite clear why this case should have been classed as "normal."

Of the five paratyphoid infections, four showed mild reddening disappearing after one day. One case was negative.

The isolated case of paratyphoid infection exhibited no reaction.

Of the three typhoid cases, one had had typhoid fever the summer previous (Widal at present 1 to 150), and gave a marked reaction, still present after four days. One had had typhoid fever a year before (Widal at present 1 to 50), and showed great swelling and reddening persisting after two days. One case was still in the hospital (April 1) convalescing from a severe infection of the preceding year, but showed no reaction (Widal at present 1 to 300).

No fresh case of typhoid was studied, owing to the great dearth of material, but if one is to judge from the behavior of the third case above described, one would be inclined to regard the reaction not as an aid in the diagnosis of typhoid fever, but rather as a sign of immunity, of acquired resistance against the infection.

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We have studied seven cases of typhoid fever and sixteen other patients admitted with varying diseases to Dr. Musser's ward in the Presbyterian Hospital. Our method varied from that described by Link in but one minor detail, as we used three sacrifications, two of which were inoculated and the central one being left for control. In no instance was there any constitutional disturbance, nor was the local effect more annoying than a temporary itching. A reaction was considered positive when there was a more intense reddening than in the control scarification, the reddening persisting for two or more days.

TABLE I.

No.	Patient.	Diagnosis.	Reaction.
1.	A. H. G.	Typhoid (severe) 44th day of illness. Temperature, 101°–103°. Widal negative. Blood culture positive.	Negative.
2.	J. K.	Typhoid fever (mild) 11th day of illness. Temperature, 99°–102°. Widal positive.	Positive. Present on third day following inoculation.
3.	G. F.	Typhoid fever (mild) 16th day of illness. Temperature, 98°–101°. Widal positive.	Negative.
4.	L.	Typhoid fever (convalescent). Widal positive. Patient suffering with pulmonary tuberculosis.	Negative.
5.	D.	Typhoid fever (convalescent). Widal positive.	Negative.
6.	McGl.	Typhoid fever (severe) 20th day. Widal positive. Clinical course of disease marked by severe hemorrhages. Autopsy diagnosis, typhoid fever.	Negative.
7.	E. P.	Typhoid fever (convalescent). Widal positive. Clinical course protracted.	Negative.

Of the seven typhoid cases studied, but one (No. 2) showed a positive reaction. This was a mild infection, the patient complained of few constitutional symptoms, and there was apparently little toxemia.

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TABLE II.

No.	Patient.	Diagnosis.	Reaction.
1.	S. G.	Pneumonia. Typhoid malaria some years ago.	Positive.
2.	J. M.	Pneumonia, central. Widal Negative. Never had typhoid.	Positive. (slight.)
3.	E. Q.	Pneumonia. Widal negative. Never had typhoid.	Negative.
4.	P. G.	Pneumonia. Pleurisy with effusion. Widal positive. No history of typhoid elicited.	Negative.
5.	R. M. G.	Thrombosis of optic thalamus. Never had typhoid.	Negative.
6.	J. H.	Arthritis sicca. Typhoid three times (?). Last time eight to ten years ago.	Negative.
7.	R. K.	Hyperacidity. Never had typhoid.	Negative.
8.	A. D.	Hyperchlorhydria. Never had typhoid.	Negative.
9.	A. M.	Adhesions (peritoneal).	Negative.
10.	L. F.	Chronic constipation. Never had typhoid.	Negative.
11.	J. J.	Acute alcoholism. Never had typhoid.	Negative.
12.	J. N.	Pneumonia. Never had typhoid.	Negative.
13.	J. C.	Gastric hyperacidity. Pulmonary tuberculosis. Never had typhoid.	Negative.
14.	B. W.	Bronchial asthma. Never had typhoid.	Negative.
15.	W. D.	Chronic bronchitis. Never had typhoid.	Negative.
16.	J. G.	Acute lymphatic leukemia. Never had typhoid.	Negative.

Of the 16 non-typhoid cases, but one (No. 1) gave a positive reaction. This patient claimed to have had typhoid malaria, but no more could be elicited concerning the nature of this illness.

One case (No. 2, central pneumonia) had a slight reaction. No history of a previous attack of typhoid could be obtained.

The other cases were promiscuous cases in the ward, studied as normal cases, in whom there was, at the time of the observations, no positive typhoid infection. In the remaining fourteen cases no positive reactions could be obtained.

It will be seen that the cutaneous reaction as advised by Link has but little practical use, as its value in diagnosticating existing typhoid fever is nil. The only case showing a positive reaction was a mildly ill patient, and the thought naturally arises that the reaction in this case was due to his resistance expressed clinically in a mild infection. If this is true, numbers 3, 4, 5 ,and 7 should have had a positive reaction, as they were either entirely over their acute illness or were in the stage of defervescence.

Why there should have been a positive reaction in Case No. 2 of the non-typhoid series is inexplicable. The positive reaction in Case

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No. 1 might be explained on the ground of a previous attack of typhoid fever, through which the patient had acquired an immunity, but were this the explanation we would expect to see the same in case No. 7.

From our studies we would conclude that the typhoid cutaneous reaction (Link) is valueless both in the diagnosis of typhoid fever and as a sign of acquired immunity to the disease.

April 8, 1909.

Card Specimens Presented May 13, 1909.

DR. JAMES E. TALLEY:

Multiple Abscesses of the Brain.

The case was not at all unique, but it serves to illustrate the paucity of symptoms that may be present in a severe condition. The patient had been ill, probably two months. Two days before he died the only manifestations to be found were a semistuporous condition and a fleeting rigidity of the neck. Lumbar puncture showed turbidity of the fluid, with a small number of staphylo- and streptococci. Even a few hours before death there was no paralysis, or even anything in the reflexes to help in localization of any of the abscesses. Two hours before death Dr. Shoemaker examined the eyes, and reported normal fundi, but a general ophthalmoplegia, pointing to effusion in the ventricles. The autopsy was performed by Dr. Swan. There was meningitis of the base, all ventricles were filled with a purulent material, and there were multiple abscesses in both hemispheres. There was also an abscess in the right lobe of the cerebellum. There was nothing to indicate the portal of the infection, no history of ear or nose trouble, and no other focus of infection.

DR. ALFRED GORDON:

Porencephalic Brain.

This brain comes from a negro boy, aged fourteen or fifteen years. According to the mother's account, the child was always feeble-minded. Physically, however, he presented no symptoms until he reached the age of fourteen years. At this age, while at school, he

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had a slight fall. He immediately got up, and went on playing; but the next day he was seized with convulsions, which soon became quite frequent. At times they were generalized, and at times confined to the right arm and leg. He then came under my observation. I had him put to bed under the care of a nurse; he was then having convulsive seizures every five or ten minutes, which could not be controlled. This condition lasted three days, at the end of which he died. At autopsy, the brain showed a decided difference in size between the two hemispheres. On the right side there was a decided depression in the temporal lobe, the pia dipping down deeply into this depression. No other change was found. The porencephalic condition was in the posterior temporal region, not in an area that could involve a motor pathway. During life there were no localizing symptoms concerning any special function.

One remarkable thing about this case is that this porencephalic condition was unquestionably congenital as evidenced by the undeveloped condition of the entire left hemisphere, when compared with the right, yet the boy never had a convulsive seizure until, the age of fourteen.

DR. GEORGE FETTEROLF:

(1) *A Heart with Anomalous Distribution of the Coronary Arteries.*

This specimen was obtained from the body of a woman, aged seventy-three years, in the dissecting-room of the University of Pennsylvania. The right coronary is very small, and arises above the anterior cusp of the aortic valve. It courses around the right auriculoventricular groove, and when it approaches the posterior interventricular sulcus it breaks up into small twigs of termination. The left coronary is very large. It gives off the anterior interventricular, continues on as the left auriculoventricular, and on reaching the top of the posterior interventricular groove it fails to terminate here, but assumes the role of the right coronary in that it becomes the posterior interventricular artery.

(2) *Section of a Lung in situ Showing a Healed Tuberculous Cavity.*

This specimen was accidentally found while cutting anteroposterior sections of the frozen chest. It shows plainly a large healed cavity

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at the anterior portion of the right apex, and into it is seen emptying a smaller cavity. It is of particular interest as showing the relations of the cavity to the anterior and posterior chest walls and as suggestive of what physical signs would be present.

DR. JOHN M. SWAN:

Eggs of the Jigger-flea (Sarcopsylla Penetrans).

The specimen was brought to me by a young man who, in June of last year, went to Jamaica and spent the summer on that island. After his return to this country, in the autumn, he excavated from one of his toes a mass of black material, looking like a tick. On being placed in water this mass swelled up and extruded a mass resembling eggs. Examination showed them to be eggs, which looked not unlike those of a nematode. I referred the specimen to Dr. Henry Skinner, of the Academy of Natural Sciences, who reported it to be the body and the ova of the female jigger-flea. This flea, it appears, embeds itself, after impregnation, in the subcutaneous tissues of the human host, where it goes on developing until it appears to be nothing but a large sac filled with eggs, though at one end the head and the anterior feet are sometimes recognizable. After a time the cyst ulcerates, and the eggs are deposited in the soil. The wound produced by the ulceration following the rupture of the sac is frequently the portal of entrance for the tetanus bacillus, on the one hand, and for bacteria which may produce a fatal septicemia, on the other hand.

DR. JOSEPH MCFARLAND:

This flea is the real jigger; but there is widely distributed in this part of the world a tick, also erroneously called the jigger, which is familiarly known as the blackberry tick. I was surprised to find that in Iowa it is universally known as the jigger.

It is found in association with blackberries and small grasses, especially if there is any dampness. It does not burrow into the skin, but it has a long proboscis, which it deeply embeds in the flesh. The poison injected into the tissues causes them to swell until the body of the tick is almost covered, the tick projecting as a minute red point on the surface of the papule. What the life history of this tick is, is

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unknown. Dr. Henry Skinner once asked me whether I thought the tick was committing suicide, because there seemed to be no purpose in its leaving the ground and embedding itself in the skin, except to be scratched out.

DR. A. J. SMITH:

Some of these insects require blood for the development of their eggs, and they probably embed themselves in other animals than man, who is best able to scratch them out. They are quite able to let go of themselves after they have filled themselves with blood sufficiently. If a little butter or other oily material is placed upon them so as to cover their breathing pores they will also drop off. If, however, an attempt is made to pick one out, its head will very likely pull off and the body remain behind, frequently setting up a suppuration.

DR. NATE GINSBURG:

Parathyroids and Tuberculous Lymph Nodes, Macroscopically Resembling Each Other.

This specimen is a thyroid gland attached to the larynx, and was removed from a colored man, who died of pulmonary tuberculosis, and whose lungs have been exhibited by Dr. Fetterolf. They showed numerous tuberculous cavities. The specimen presents a number of enlarged lymph nodes surrounding the thyroid gland, and shows the necessity for differentiating between the parathyroids and these enlarged lymph nodes. A number of writers have stated that they have observed parathyroids on all aspects of the thyroid gland, but I have never found them in any but the normal position; and I do not believe that they exist any more irregularly than do other ductless glands in the body. We made sections of one of the parathyroids, and found no tubercles present. The manner of differentiating macroscopically lies in the position of the parathyroids, and in the fact that they have a distinct color and separate artery, which invariably comes from the inferior thyroid artery. Much to my surprise, I recently read that tuberculosis of the parathyroid bodies had been frequently observed by foreign pathologists, who called attention to the frequent occurence of Chvostek's sign in tuberculosis occurring in children. It is possible that the structures examined were tuberculous lymph nodes which were mistaken for parathyroid glands.

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The Nature of the Arteriosclerotic Process.

BY J. GEORGE ADAMI, M.D., F.R.S.,[1]
MONTREAL, CANADA

SURELY all of us who are active pathologists have been impressed by the fact that the more autopsies we perform the larger does arteriosclerosis loom as the fundamental morbid process in the majority of deaths after the age of forty years. If trauma, malignant disease, and infections, such as pneumonia and the rarer tuberculosis, be eliminated, we are left with that vast mass of cases of cardiac incompetence, aneurysm, chronic bronchitis and emphysema, cerebral apoplexy, and chronic Bright's disease; and the more we study these cases the more it is borne in upon us that in these the terminal event is but an outcome of the one common underlying process of

[1] Address at the Annual Conversational Meeting, April 22, 1909.

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arterial disease. At the same time, the more carefully we study the arteries in these cases the more we recognize that we deal with an almost protean series of disturbances; now it is the upper portion of the aorta, the ascending limb, or the arch that shows the most pronounced and obvious lesions, now the abdominal aorta; in other cases the aorta is relatively free from sclerotic change, but its larger branches show irregularities, this with or without pronounced involvement of the smaller arteries, which in their turn are not equally affected; at times the renal, at times the cerebral, at times those of the extremities are the seats of most advanced change. In the second place we find that the lesions are not all of one order, so much so that it may well be debated, as it is debated, whether one common name should be applied to the series. I am free to acknowledge that this name arteriosclerosis is not wholly satisfactory. Marchand[1] has recently recommended that of atherosclerosis, but this, like the older atheroma, is inadequate, in that it implies that the development of *ἀθήρη*, or a porridgy degeneration, is inevitable. Something might be said for this suggestion had we to deal only with the aorta and the larger vessels, although even in these there are developed sclerotic states—I refer to those of syphilitic origin—which do not by any means necessarily pass on to an atheromatous stage. (These Marchand would place in a separate class.) It is, however, inadmissible for the condition as found in the smaller sized arteries, in which the sclerotic change is predominant, the atheromatous or degenerative characteristically absent. Again, it may rightly be objected that the atheroma is a secondary and not a primary condition; it is always the secondary outcome of fibrosis. "Arteriocapillary fibrosis," save for its flatulency, has more in its favor than atherosclerosis, but again is incorrect, for the capillary changes are not obvious, and, as I shall point out, when present must be regarded as secondary. We come back, therefore, to this, that the term "arteriosclerosis" is the most satisfactory name that has so far been afforded for this series of arterial changes, since sclerosis, which is equivalent to fibrosis, is the condition of commonest occurrence in the series of included conditions.

[1] Verhandl. Deut. path. Gesellsch., 1906.

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What, then, are the different forms that we have to take into account? So much has been written upon the subject of late years that I need only refer to the salient points, for doubtless the majority here present have as full a knowledge of this matter as have I who speak. And first as to the main orders of disturbance seen in the aorta and its larger branches—in the vessels, as we may term them, of the elastic type:

1. Most common is the ordinary nodose arteriosclerosis. This shows itself in the slightest cases as a thickening and sclerosis, more particularly at or around the origins of the side arteries, as yellowish-white thickenings notably affecting the origins of the series of intercostal arteries. Later these have grown in size, and some may have coalesced, forming in the opened aorta projecting flattened nodes, and now these may be scattered somewhat irregularly through the aorta, tending to be more abundant and more advanced in the abdominal region. It is this form that, more particularly, passes into the condition of atheroma, and of calcification of the intimal plaques.

2. Almost as frequent is a contrasted order of disturbances, in which clinically we have the most obvious proof of the existence of arteriosclerosis, in the presence of hardened and at times pipe-stem radials; but when we come to examine the aorta we may in the most typical cases find a complete absence of nodose thickening of the intima. In its place there is a diffuse dilatation of the aorta, affecting more particularly the thoracic portion. Instead of being thickened, the aortic wall appears to be thinned and the increased volume of the tube tends to show itself not only in breadth, but also in length, the vessel becoming somewhat tortuous; the arch takes a wider sweep, the abdominal section is curved. This I am inclined to regard as the uncomplicated senile type of the disorder. It is further characterized by the presence, in the common iliacs and the carotids, of slight depressions, tending to have their long axis situated transversely, in fact, by the very reverse of the sclerotic nodosities, a giving way taking the place of thickening of the wall. And the question may well be asked, Should this be included? It is not a sclerosis, but merely a degeneration. This I freely admit, but would urge that the condition of the whole arterial tree has to be

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taken into consideration in making our diagnosis, and if we do this we find that in these cases the smaller arteries are markedly sclerotic, with localized areas of intimal fibrosis, with hypertrophy and fibrosis of the middle coat and often with well pronounced periarterial fibrosis. The sclerosis of the radials and other middle-sized arteries, often so prominent in these cases, is paradoxically not a sclerosis proper; it is not necessarily due to fibrosis of the intima or other coats. Sometimes there is a diffuse thickening of the intima of moderate grade, but that is not the cause of the hardening. As Dr. Klotz[1] has most serviceably pointed out, the essential change in vessels of this type is a calcification of the media, which I may add, following Russell,[2] is apt to be preceded by a marked hypertrophy of the middle coat. For convenience, I would speak of this order of arteriosclerosis as Moenckeberg's sclerosis, Moenckeberg[3] having been the first to make a full study of what is the most striking feature, namely, the areas of giving way and slight sacculation seen in the main branches of the aorta due to degeneration of the media. But, doing this, I would impress upon you that uncomplicated examples of this order of disturbance are relatively uncommon. Quite the commonest condition in elderly people is a combination of these two types, having occasional nodes or plaques of sclerosis or atheroma in the aorta, more particularly in its abdominal portion, though by no means necessarily confined to this region, with this faint saccular giving way in the common iliacs and carotids, suggesting strongly that the same order of events leads now to the one, now to the other development; that, in fact, they are diverse manifestations of a common state.

3. The third great type is the syphilitic. The aortic manifestations of this form are in the broad features so much of the same order

[1] Calcification of the Aorta in Rabbits after Injection of Adrenalin, Journal Exp. Medicine, 1906, viii, 325; Calcification of the Media in Arteries of the Elastic tissue Type, Journal Exper. Medicine, 1906, viii, 330; The Relationship of Experimental Arterial Disease in Animals to Arteriosclerosis in Man, Journal Exper. Medicine, 1906, viii, 304; Experimental Arteriosclerosis, British Medical Journal, December, 1906; Experimental Work-Arteriosclerosis, Montreal Medical Journal, March, 1908, and Centralbl. f. allg. Pathol., 1908, xix, 535.

[2] Arterial Hypertonus, Sclerosis, and Blood Pressure, Edinburgh, 1907.

[3] Virchow's Archiv, 1903, clxxi, 141.

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as those of ordinary nodose arteriosclerosis that it is only during the last generation and, indeed, during the last seven years that the distinguishing features have attained general recognition. Thanks to the labors of Dohle,[1] of Kiel, and other pupils of Heller, and of Chiari,[2] we now have no difficulty in making the distinction, if not always by the naked eye, then surely under the microscope. The seat of election in the first place is in the ascending aorta and arch, and here the nodes are liable to lie in groups. These in their earlier stage are large and, if I may so express it, succulent, with a semi-translucent or hyaline appearance; characteristically they have little tendency to atheromatous and calcareous change, but, on the contrary, exhibit a later scarring or central depression with some puckering. The reason for this is found upon microscopic examination. The primary disturbance here is subacute mesaortitis, with small-celled infiltration around branches of the vasa vasorum and absorption of the elements proper of the media. Coincidently there is overgrowth of the intimal tissues, an when, as a result, the deeper portions of the overgrowth exhibit necrotic change and degeneration, then the underlying inflammatory granulation tissue advances new capillaries into the necrotic area. The result is an absorption of the degenerated material, replacement by cicatricial tissue, shrinkage, and scarring. So far as my observations go, there is a striking lack of vascularization and replacement in the ordinary nodose arteriosclerosis. It does not occur during the necrotic atheromatous stage; I have encountered it when there is already pronounced intimal calcification and the necrotic change is extending into the inner layers of the media.

Here in connection with syphilis, and yet more markedly, there is to be observed that same paradox seen in connection with the Moenckeberg type; while the syphilitic virus leads to the more pronounced intimal overgrowth, at the same time it leads characteristically to the opposite condition of lack of intimal overgrowth, thinning of all the coats, and aneurysm production. It will be familiar to you that modern workers, with the exception of von

[1] Inaug. Diss., Kiel, 1885.

[2] Präger med. Woch., 1906, xxxi, No. 12; Verhandl. Deut. path. Gesellsch., 1904.

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Hansemann, ascribe from 60 to 85 per cent. of aneurysms to syphilis. How are we to reconcile these opposing results?

These are the main types. Acute changes do not come under the heading of arteriosclerosis, nor do simple degenerative changes without proliferation. The fatty streaks of the intima seen often after acute infection, are not here included, although these and certain other intimal changes may throw light on certain phases of the process. To them I shall refer later.

Turning now to the other arteries, we may, as regards arteriosclerotic change, divide them into the muscular arteries and the arterioles. As regards the former, the same changes, the ordinary thickening of the intima, the giving way of the Moenckeberg type, and the syphilitic changes may be seen as in the aorta, with, however, one of two modifications which would seem to be a function of relative size. Thus, we do not encounter anything like the same extent of atheromatous and degenerative change. Compared with the size of the artery, the areas of intimal thickening may be extreme; nevertheless, in absolute size they do not compare with the plaques seen in the aorta. And it may be reasonably suggested that degeneration when it occurs is due to cutting off of the nutritive lymph supply by the development superficially of layer after layer of dense new connective tissue, and that in general the size of those plaques in the arteries (save in the larger cerebral vessels and the coronaries) is not sufficient to inhibit the percolation of lymph and arrest of nutrition of the more central areas. This does not, however, mean that there may not be extreme calcification, more especially in the middle sized arteries; only that calcification affects, more particularly not the intima, but the media.

This brings us to the second point of difference, namely, that in these arteries the media exhibits much more obvious alteration. Where there are relatively large plaques of intimal thickening there beneath them, even with the naked eye, the media is seen to be notably thinned. But, on the other hand, it may exhibit diffuse thickening from hypertrophy of its muscle tissue, with little obvious intimal change. On the other hand, there may be degeneration of the muscle and replacement by connective tissue; in some regions this may be associated with giving way and dilatation of the arterial

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lumen with associated intimal thinning; in others there is seen a more or less diffuse thickening and overgrowth of the intima, suggesting compensatory change. Passing to the *arterioles*, we find, it is true, the same series of changes, but here the relationships are significantly altered. There has been active debate as to their significance and relative frequency. In one order of cases the muscular hypertrophy of the middle coat has been the dominating change. This is especially well seen in certain kidneys, so much so that sundry observers have laid stress upon this as the cardinal change. In another series fibrosis is the most evident alteration—fibrosis of the *intima*, fibrosis replacing largely the *muscular* tissue of the *media*, fibrosis and pronounced overdevelopment of the *adventitia*. So that other observers have waved the muscular change to one side and regarded the fibrotic change as the all-important condition.

Yet another state has also been dwelt upon, particularly in association with the infectious type, as seen in tuberculosis, syphilis, and chronic glanders, namely, the active cellular proliferation of the intimal endothelium leading to an obliterative endarteritis. It is still unsettled whether this proliferation is directly connected—as Baumgarten believes it to be—with the production of the intimal fibrosis—whether, that is, the endothelium directly gives origin to the connective tissue overgrowth of these arterioles, or whether the processes are distinct. Provisionally, I incline to Baumgarten's opinion.

How now are we to harmonize and bring into a common scheme these various lesions? What, in short, is the fundamental underlying change—if there be any—common to the different conditions? The answer to this question can be approached in two ways—either by an exhaustive analysis of the factors seen to be in action in the various types of arteriosclerosis; or by taking one form in which the causative factors have been most fully determined and applying the results gained from the study of this form to the other cases, to observe whether any common general principles are capable of application to all. Both, I believe, lead surely to the same end result, and let me confess that I have been puzzled as to which method to employ. It seems to me, however, that the former would consume too much time; it would demand a preliminary discussion of

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the minute anatomy of the arterial tree, of the physiology of the same, of the regulation of the blood pressure, and the influence of contraction of the arterioles upon the aorta and the aortic conditions. It is true that, employing the other method, reference must be made to most, if not all, of these matters, but I imagine that it will be less wearisome if I take up a concrete case and then proceed to apply the results gained from that to a consideration of the other cases.

Now undoubtedly we possess the clearest and most indubitable data regarding the syphilitic form. There is no question nowadays that the primary lesion in syphilitic aortitis is a granulomatous condition or small-celled infiltration immediately surrounding the terminal vasa vasorum in the media; the primary condition is, as Chiari describes it, a syphilitic mesaortitis, and this involves in the first place the outer half or two-thirds of the aortic media. Certain of the vasa only are affected. Here, just as in acute mycotic aneurysm, as shown by Dr. J. McCrae's[1] study of a case published from our laboratory, the infective agent gains entrance into and lodgement in particular vasa. And here it may be noted that several observers have discovered the spirochete in the aortic lesions. With this infiltration there is, as Dr. Klotz points out in an article shortly to be published, a remarkable dissolution of the elements of the media. They seem literally to melt away. This explains the thinning and depressions which may occur, so that, as Aschoff points out, placed against the light these areas are semitranslucent. To what an extent this process may extend is well shown in the accompanying specimen (Fig. 1) which Dr. Klotz has been so good as to permit me to demonstrate to you. This has been stained to demonstrate the elastic tissue. You will observe that in the region where there is the most extensive small-cell infiltration the elastica has completely disappeared.

I will not say that this dissolution is specific. I do not believe that it is. I am inclined to think that it may be the outcome of local inflammation, due to more than one cause, with swelling, degeneration, and necrosis of the cells of the involved area. But undoubtedly

[1] Journal Path. and Bact., 1905, x, 373.

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the most frequent cause is syphilis. Here, therefore, is the onset of the syphilitic or mycotic type. It will be readily understood how such extreme destruction of the media, the main sustaining coat of the aorta, leads on to aneurysm. In fact, we may say that it is universally acknowledged nowadays that degeneration of the middle coat is the dominant cause of aortic aneurysm. But such extreme destruction of the middle coat as here shown is the exception and not the rule; so again in syphilitic aortitis aneurysm production is

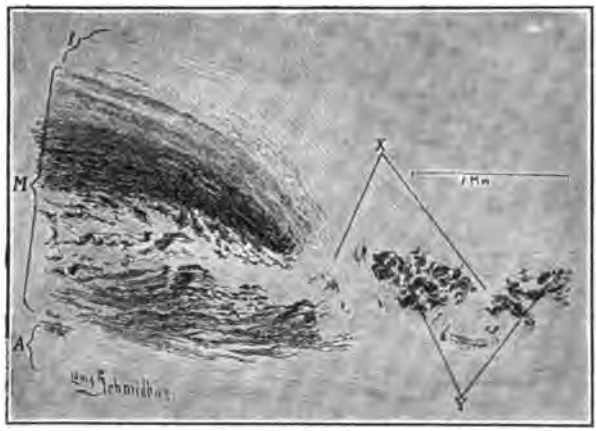

FIG. 1.—Section from a case of syphilitic mesaortitis stained by the elastic tissue stain to demonstrate the extraordinarily degenerated and diseased appearance of the elastic tissue through syphilitic mesaortitis. It will be seen that at *X* the elastic fibers have completely disappeared; at *Y* they are reduced to irregular masses. There is some definite hypertrophy, both of the intima, *I*, and of the adventitia, *A*, but this has been insufficient to prevent a certain giving way of the wall. (From a specimen prepared by Dr. Klotz.)

the exception; what is far more common and widespread is the production of intimal thickening. How is this to be explained? I doubt if there be any more obvious example of compensation in the whole of pathology; degeneration of the one coat, the media, is accompanied or followed by overgrowth of the other, the intima; nay, more, as Dr. Klotz's example illustrates very beautifully, and as I confess I had not previously realized, in connection with the

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aorta there may[1] be a coincident and very pronounced hypertrophy of the adventitia (Fig. 1).

Certain points stand out very prominently regarding this intimal thickening. In the first place, it exhibits none of the ordinary ear-marks of an inflammation. There is no formation of granulation tissue properly so-called; no new vessels; no small-celled infiltration, and, notwithstanding this, the new connective tissue formation attains to large proportions. The intima, it is true, is in itself non-vascular; it receives its nourishment by diffusion from the plasma within the aorta, as, indeed, would seem to be the case with the innermost layers of the media. But if we take any other non-vascular region, the cornea for example, and induce in that an inflammation by any of the accepted methods—by the injection of bacteria or the employment of caustic agents—within a short time new vessels make their way to the injured area from the periphery. Save as a late event, as already noted, we do not encounter this in the intimal thickening in syphilis even when there is an active granulation tissue formation in the media. This is a very remarkable fact; the intimal overgrowth is essentially and purely hypertrophic. The internal elastic lamina constitutes as it were a barrier. We do not deal with an endarteritis, and Virchow was wrong in labelling it with this name; as again have been Thoma and other later writers (Fig. 2).

But if an hypertrophy, how is it to be explained? We owe to Thoma,[2] in connection with ordinary arteriosclerosis, the first clear recognition that this is a compensatory hypertrophy—that in ordinary arteriosclerosis there is first a giving way of the media, and that the intima proliferates as a consequence. Thoma sought to explain this overgrowth as of nutritive origin, as due to alteration in the rate of blood flow at the region of bulging of the arterial wall. For myself, I must confess that I have never been able to grasp his explanation; what is more, I have never met anyone who has pretended to do so. Thirteen years ago, in an address before the

[1] Since this address was delivered J. H. Wright and O. Richardson have also called attention to this thickening of the adventitia with extensive necrosis of the media. Boston Medical and Surgical Journal, 1909, clx, 539.

[2] Virchow's Archiv, civ, and subsequent volumes.

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New York Pathological Society, I afforded an explanation.[1] That also was not comprehended at the time. For example, Professor Mott[2] wholly mistook its drift. But I am more and more convinced that that explanation was rational, and, what is more, recent studies of a different nature have afforded a brilliant demonstration of its correctness. I laid down then that this regular development of layer after layer of new connective tissue was non-inflammatory,

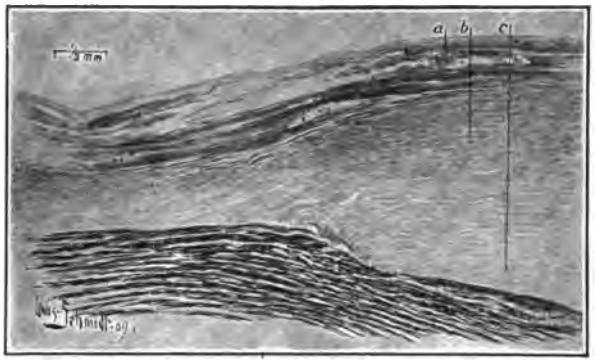

FIG. 2.—Section of an aorta from syphilitic mesaortitis with some narrowing of the media and great overgrowth of the intima. It will be observed that the layers of new tissue of the intima show a regular arrangement with absence of vessels and of small cell infiltration. The outer layers, at *a*, in this case exhibited pronounced fatty change. The intermediate layer, *b*, took on a slight stain with the elastic tissue reagent, and under the high power this was seen to be due to the fine fibrils of what, from their arrangement, were young connective tissues, taking on the elastic tissue stain. Deeper down, at *c*, there was a complete absence of this reaction. The media, on the contrary. while narrowed, stained deeply with this stain. (From a specimen prepared by Dr. Klotz.)

but was of the nature of *strain hypertrophy*—that just as increased pull or strain of the muscles upon their bony insertions leads in athletes to an increased development of the bony ridges, to a localized hypertrophy of bone, so within certain limits, increased tension or pull upon fibrous connective tissue favors its overgrowth, provided that adequate nourishment be afforded at the same time. It is

[1] On the Relationship between Inflammation and Sundry Forms of Fibrosis, Middleton Goldsmith Lecture, Medical Record, 1896, pp. 469 and 505; see also Discussion upon Arteriosclerosis, British Medical Journal, December, 1906, ii.

[2] Allbutt's System of Medicine.

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but another example of the law, wholly misunderstood by Weigert, that increased functional activity within certain limits favors growth. I am glad to see that Professor Aschoff[1] explains the progressive

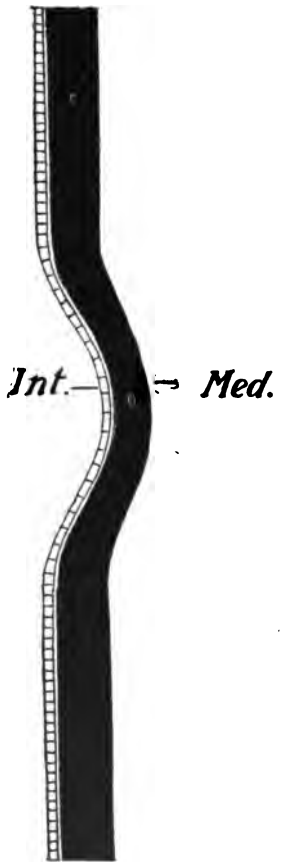

FIG. 3.—Schematic representation of the increased strain brought to bear upon the cells of the intima, *Int.*, when the media, *Med.*, undergoes a localized expansion through relative weakness.

increase in the elastic tissue of the aorta as being due to a like-work hypertrophy.

I held, and so I still hold, that a moderate local giving way of the

[1] Beihefte zur med. Klinik, 1908, iv.

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media under the pressure to which it is subjected by the blood within an artery causes an increased strain upon the overlying intima, which must undergo a certain amount of stretching, as it now becomes pressed outward to expand over the concavity afforded by the bulging of the media (Fig. 3). Herein is the stimulus to growth, and the growth continues, layer after layer, until not, as Thoma held, the concavity is accurately filled and the lumen restored to the status quo ante, but until the volume of the new tissue and the resistance that this affords to the mean distending force balances the loss sustained by the weakened media. In other words, when the resistance offered by the whole arterial wall at such a locality is equivalent to that of the rest of the aortic or arterial wall, then the strain is reduced and the process of hypertrophy becomes arrested. In these cases the youngest tissue is situated immediately beneath the endothelium, the oldest, most remote, and nearest to the deeper musculo-elastic layer. Unlike what occurs in the ordinary form of arteriosclerosis, in syphilis this latter layer, so far as I have seen, shows comparatively little hypertrophy.

The convincing demonstration of the accuracy of this view has been afforded by one of Carrel's remarkable transplantation experiments. Carrel,[1] it will be remembered, removed a length of the cat's carotid and replaced it by a length of vein from the same animal and of approximately the same caliber; under the increased blood pressure the vein exhibited dilatation, but left in situ for many weeks it presented at the end of the period a remarkable connective tissue hypertrophy of all its coats, so that its eventual thickness was distinctly greater than that of the artery at either end of the transplanted piece. The adequate and, in fact, as I freely admit, improved nutrition to which the vein is subjected, might by some be held to explain the hypertrophy of the intima, but at the same time the more that becomes sclerosed, the less becomes the nutrition of the deeper layers; but all the coats showed the connective tissue overgrowth. Add to this that cases in which increased nutrition, pure and simple, leads to hypertrophy are almost if not entirely, wanting. I can bring to mind no single incontrovertible example. There is, I

[1] Journal Experimental Medicine, 1908, x, 130.

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hold, no other satisfactory conclusion than that in this case it is the increased strain thrown upon the venous wall (coupled with adequate nutrition) that leads to the profound connective tissue hypertrophy.

When, on the other hand, the destruction of the media is more widespread, and we must presume more acute, then, as in aneurysm formation, we encounter not intimal overgrowth, but the reverse. In other words, the expansion of the intima which has wholly lost its main support, the media, is now so great that we pass from the state of *strain* to that of *overstrain*, and now with the overstrain in place of hypertrophy we tend to get atrophy.

We thus arrive at the following conclusions regarding the effects of syphilis upon the aorta: (1) The primary disturbance is a granulomatous, inflammatory degeneration of the media; (2) this leads to a local giving way of the aorta; (3) if this be moderate it results in a strain hypertrophy of the intima and of the adventitia, with the development of a nodose intimal sclerosis; (4) if it be extreme, there results, on the contrary, an overstrain atrophy of the intima and aneurysm formation; (5) the intimal nodosities are here not of inflammatory type and are non-vascular, although, with the progressive laying down of layer upon layer of connective tissue on the more internal aspect of the intima, the earlier and deeper placed layers of new tissue gain less and less nourishment, and so are liable to exhibit fatty degeneration and necrosis; (6) these products of necrosis exert a chemiotactic influence upon the nearby vessels of the medial granulation tissue, with, as a result, (*a*) a secondary and late entrance of new vessels into the early and deeply placed atheromatous area; (*b*) absorption of the necrotic products; (*c*) replacement by granulation tissue; (*d*) contraction of the granulation tissue; and (*e*) depression and scarring of the sclerotic nodules so characteristic of syphilitic sclerosis.

Can we apply these deductions to ordinary non-syphilitic nodose arteriosclerosis and to the Moenckeberg's type already noted? I think we can, or otherwise, and this is the crucial point, we can demonstrate that the ordinary arteriosclerosis of advancing life exhibits a primary giving way of the media, and we can do this both histologically and by experiment. First, as regards the histology, a most interesting study has been published recently by Professor

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Aschoff regarding the progressive changes that are undergone by the aortic media in the course of life. I will not go into all the details, but merely epitomize his main conclusions. In infancy the elastic laminæ of the media stand out sharply defined, well separated from each other by the muscle layers, which are well developed. There is, that is to say, sharp alternation of muscle and elastic layers. From childhood there is to be observed a slow progressive increase in the elastic elements of the media. Not only do the individual lamellæ seen in cross-sections become thicker, but also they afford an increasing number of fine secondary filaments feathering off from these and crossing the muscle layer, so that now they are no longer sharply defined, but more ragged upon cross-section. This progressive increase attains its maximum at or about the age of thirty-five, and from now on for the next fifteen years the condition is relatively stationary. After fifty, according to Aschoff, there is to be observed a slowly progressive atrophy of the elastica. The media becomes obviously thinner and presumably weaker.

Independently, Dr. Klotz has been studying the same subject for some years and for the last twelve months Mr. Foster, under his direction, has examined a long series of aortas, from those of infancy up to those of advanced age. His work is on the eve of publication. Again, not to enter into details, I may say that these observers are wholly in agreement with Professor Aschoff's findings up to the age of thirty-five and in practical agreement up to that of fifty. But, as Klotz has already pointed out on more than one occasion, the subsequent degenerative process is one showing itself histologically, not so much in connection with the elastic lamellæ as with the intervening muscle. This from the age of thirty-five onward begins to exhibit fatty degeneration, although, it is only after fifty that, as a rule, this becomes at all marked. And now one or both of two processes may occur. Either, as shown by Klotz's admirable studies, the fatty gives place to a calcareous infiltration, fine calcareous granules appearing in the course of the muscle fibers—a sign of necrosis of these fibers—or they undergo complete absorption. Perhaps most frequently both processes are to be made out. As a result the intervening spaces between the elastic lamellæ become smaller and smaller, and often there is afforded the appearance of

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thick lamellæ due to the approximation of two or more, which can be resolved under higher magnification. With this, whereas in the young aorta the lamellæ are wavy, due to the contraction of the intervening muscle fibers, now they are relatively straight. It is this muscular atrophy rather than atrophy of the elastic tissue that thus would seem to be the main cause of the thinning of the aortic media. I do not in the least mean to say that the elastica is unaffected in this process. At times the calcareous degeneration affects it also. Everything indicates that coincidently it *loses its elasticity*, becomes more rigid and more expanded as the result of internal pressure; it is inapt to return to its former length.

It is further to be noted that the calcification is unequally distributed. Frequently in Dr. Klotz's specimens of the Moenckeberg type it is most marked, and the thinning of the media is coincidently most pronounced in the walls of the shallow sacculations already noted. The presence of the sacculations show that here are the regions of greatest weakening. But it is frequent to find that when there is marked nodose thickening of the intima then also the underlying aortic media is thinned. This, it is true, is most evident not in the aorta, but in its branches—in the carotids, the splenic artery, the coronaries, etc. In all of these there may be an extraordinary overdevelopment of the fibroid intima and an equally striking expansion and giving way of the media. All must be familiar with specimens showing this condition. On the other hand, it has to be admitted freely that there may be well-marked intimal nodes of the aorta when the underlying media shows no recognizable thinning. Apart from possible exceptions to be subsequently noted there is an explanation to be afforded for this state of affairs—an explanation along the lines of Thoma's well-known observations upon the disappearance of the projecting intimal nodosities when the aorta is filled with melted lard under pressure. This is most rapidly afforded by the accompanying diagram (Fig. 4), which represents a length of aortic wall, in which the midportion has become weaker than the rest. This portion under internal pressure will be liable to give way, and, while thus bulging, will of necessity exhibit a definite grade of thinning, with compensation or strain overgrowth of the intima tending to fill the concavity. If, as occurs postmortem,

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the internal pressure be removed, then the natural elasticity of this midportion of the wall, which has not been wholly lost, will result in a disappearance of the concavity, the wall now appearing to be of normal thickness of media with a projecting nodosity of the intima. The same will naturally appear in sections prepared under the same conditions.

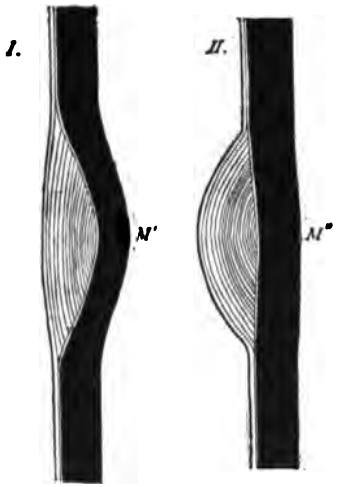

FIG. 4.—*I*, media weakened at *M'* with overgrowth of intima filling in the depression. *II*, with postmortem rigor and contraction of the muscles of the media and removal of the blood pressure from within, the stretched media at *M''* contracts; the intimal thickening thus projects into the arterial lumen.

Let us now turn to the experimental evidence. The active discussion as to whether the lesions caused by adrenalin, barium chloride, nicotine, and other drugs in the rabbit are to be regarded as in any way equivalent to arteriosclerosis as seen in man will be familiar to all of you, and many of you may have come to very definite conclusions upon the matter. Certainly these lesions do not resemble the ordinary nodose arteriosclerosis, but, as all must admit, the constant feature is a giving way of the middle coat, and this to such an extent that at times definite aneurysmal pouches are produced, at others and frequently those more shallow sacculations, scarce to be designated as aneurysms proper. As Klotz and K. Ziegler[1]

[1] Ziegler's Beiträge, 1905, xxxviii, 229.

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independently pointed out, the appearance is identical with that noted by Moenckeberg in his type of arterial change. Medial degeneration and giving way is the dominant lesion of adrenalin

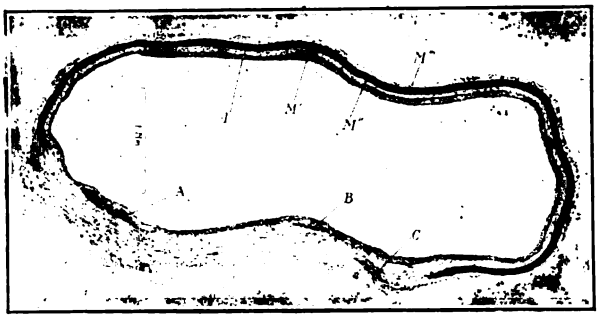

FIG. 5.—Section through the aorta of a rabbit that had been suspended for three minutes daily by the hind legs, for one hundred and thirty days, to demonstrate dilatation and relative absence of intimal proliferation. Around the greater part of the organ there is pronounced thinning of the media with calcareous degeneration of the middle layer (*M''*). This dilatation and thinning are less marked round about one-third of the organ, and here there is a slight grade of patchy hypertrophy of the intima at *A* and *B*. This hypertrophy here particularly involves the deeper musculo-elastic layer. At *C* there is beginning calcification of the media. (From specimen stained with Sudan III and silver nitrate by Dr. Klotz.)

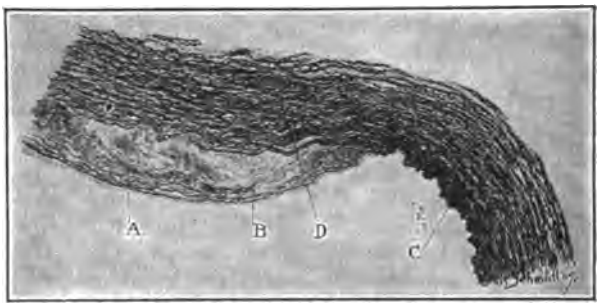

FIG. 6.—Section from the carotid of the same rabbit (higher magnification) exhibiting at *A* well-marked nodular sclerosis of the intima. At *B* the deeper layers of the hypertrophied intima are already showing degenerative changes. *C*, normal intima. *D*, media. (From a specimen by Dr. Klotz.)

disturbances. I took occasion to point out at the discussion on arteriosclerosis, at the Toronto meeting of the British Medical Association in 1907, that the reason for the lack of intimal overgrowth

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might well be the acute development of the medial degeneration, resulting in rapid expansion of the intimal sheath and overstrain rather than strain, and I suggested that less extreme degeneration would be found to result in a more typical arteriosclerosis with intimal hypertrophy. Since then Dr. Klotz, by a different method, has demonstrated the truth of this surmise on my part. He has set up arterial disease in the rabbit without the use of any drug whatsoever, and that by merely suspending a (previously) healthy well-grown buck for three minutes daily by the hind legs, head downward. This naturally caused, *pro tem*, an unaccustomed blood pressure in the thoracic, cervical, and cranial vessels, a reduced pressure in the abdominal and other arteries of the hinder end of the body. After this is continued for one hundred to one hundred and twenty days the heart is found greatly hypertrophied, the arch and the thoracic aorta are dilated, with very distinct thinning of their walls; the abdominal aorta, on the other hand, is unaffected; the carotids are larger than normal, and this is the important point—they exhibit a typical irregular intimal sclerosis. There is pronounced connective tissue thickening of that intima.

These results can only be explained in one way, namely, as the effects of the daily temporary sudden increased blood pressure brought to bear upon the vessels of the anterior half of the body.

That has resulted in diffuse dilatation of the larger vessel, the aorta, without intimal overgrowth, and in pronounced intimal overgrowth of the smaller vessels, the carotids. Here for the first time, I think, we have an absolute demonstration that one and the same cause is responsible for the two orders of conditions, the demonstration that the arterial thinning of the Moenckeberg type and the intimal thickening of ordinary (senile) arteriosclerosis are diverse manifestations of a common process. The greater circumference and the relatively slighter resisting or accommodative force of the aortic wall due, I may say, to its anatomical structure, has led to overstrain and dilatation, and as a consequence absencce of intimal proliferation the lesser circumference of the carotids and their proportionately greater resisting strength has been followed by a relatively slighter dilatation, tending to be localized to particular areas, and here

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as a result there has been strain, not overstrain, of the intima and a resultant connective tissue hypertrophy. I must add, in justice, that another Canadian worker, Dr. Harvey, of Toronto, continuing work begun under Professor J. J. MacKenzie, has independently in the laboratory of Professor Dixon, of Cambridge, England, brought about the same diffuse dilatation of the aorta and cardiac hypertrophy by temporary digital compression of the rabbit's aorta extending over long periods. He does not, however, in his communication call attention to the coincident sclerotic change in the smaller vessels.[1]

Here then we arrive at a common order of events in the two great types of aortic sclerosis—the syphilitic and the ordinary nodose forms. In both we find weakening of the media as the primary disturbance; in both, if this be above a certain grade, there is pronounced giving way without intimal compensation; in both, if below this grade, a strain hypertrophy of the intima is manifested, leading to the production of intimal thickening. Only, in syphilis the giving way of the media is the more extreme, and so we more frequently encounter advanced aneurysmal formations as contrasted with the shallower sacculations of the Moenckeberg type, and in this, also, occurring as a rule earlier in life, there is a more exuberant regenerative power exhibited by the intima.

This view, it will be seen, demands that strain or pressure is the cause of the intimal overgrowth in both orders of disturbance; it demands also that the giving way of the media in the first place is due to a local weakening sufficient to render the arterial wall unable to resist the outward thrust of the column of blood. Nay, more, Klotz's experiment shows that increased intravascular pressure alone may be the cause of the medial degeneration and weakening in the first place, of the giving way of the arterial wall in the second, and of the intimal hypertrophy in the third. We are brought thus face to face with the time honored problem—to what extent is heightened arterial pressure—or, as Sir Clifford Allbutt would seek to have us call it, *hyperpiesis*—a factor in arteriosclerosis?

[1] Personal communication from Professor MacKenzie and Sir Clifford Allbutt. I was of the impression that Harvey's results had been published, but can find no reference in the Index Medicus or elsewhere.

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From the data already afforded, it is evidently not an essential factor in the syphilitic cases. Undoubtedly when present it may accelerate the process in these, but infection is here the primary agent in causing the atrophy and absorption of the media.

As regards senile arteriosclerosis, the observations of Aschoff, Klotz, and Foster show that after fifty there is to be determined a physiological atrophy of the media; obviously the degeneration of the muscular layers and the further indications of change in the elastic lamellæ indicate a weakened media. It is not necessary in these cases to demand an increased blood pressure. The normal blood pressure must eventually be adequate to cause giving way of the media with or without consequent intimal hypertrophy.

Granting this for senile cases, then for the presenile arteriosclerosis, we are, from Klotz's experiment, forced to recognize that high intra-arterial pressure, and this alone, is sufficient to bring about a nodose arteriosclerosis with all its possible dangers. That experiment affords the experimental proof of the danger of heightened blood pressure, which from practical experience clinicians have so learned to fear—and this in a perfectly clear manner, with no ambiguities or possibilities of lack of appreciation of other factors. High pressure, and high pressure only, can be invoked to explain the results which I have demonstrated to you.

We then reach the following conclusions, namely: That *like results may ensue when, on the one hand, the artery has undergone weakening and the blood pressure is normal, and when, on the other hand, the artery has no preliminary degeneration of its media and the blood pressure is above the normal.* What is of importance is that, as shown by this experiment, it is not necessary to have a blood pressure which is permanently above the normal; an acute rise for a short period frequently repeated will bring about the result.

I would greatly like to enter into a discussion of the mechanism of increased arterial pressure in relationship to peripheral arterial sclerosis, but have already taken so much of your time that I can venture at most to suggest the headings. I would call your attention to the fact that it is the arterioles through the body and their tonus that determine the existence of the normal blood pressure; that heightened blood pressure in the larger vessels means increased

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contraction of the arterioles of important areas; that thus to changes in the arterioles and smaller arteries we must eventually look for the explanation of hyperpiesis; that it is by contraction of the arterioles that adrenalin, digitalin, barium chloride and the other raisers of blood pressure produce their effects; that in this contraction we have the elements necessary for the establishment of a vicious cycle; that, as shown by Leonard Hill, the arteries react normally to increased internal pressure not by dilatation, but by contraction; that thus the higher the blood pressure the more contracted do the smaller arteries tend to become, and that so, if the heart responds to the increased work thrown upon it, the higher still becomes the blood pressure. Along these lines it will be seen that rise of blood pressure tends in the first place to throw increased work upon the musculature of the smaller arteries; tends, that is, to cause their hypertrophy; if the rise is progressive, then this hypertrophy gives place to exhaustion, muscular degeneration, and dilatation of the arteries (and arterioles). As a result, strain hypertrophy of the intima shows itself with thickening, and it may also be of the adventitia, resulting in chronic periarteritis. And now, with continued degeneration of the medial muscle in those muscular arteries, fibrosis of the media may also show itself. I would thus regard muscular hypertrophy of the arteries and fibrosis of the different coats as different stages in one and the same process. Whether these peripheral changes are the more marked, or the central, depends, I would suggest, upon the relative resisting power of the elastic and the muscular arteries of the individual respectively.

Lastly, it may be asked, have I included here all the forms of arteriosclerosis and intimal hypertrophy? I certainly believe that I have referred to the more important, though I have not exhausted the forms. There is, for example, a form which Aschoff would term functional sclerosis, seen in the ovaries and uterus, in the ovaries after menstruation and ovulation, in the uterus after menstruation and placentation. The sclerotic change here may be extreme, and again is of an hypertrophic and regenerative type—so much so that in the uterus there may be encountered, as shown by Sohma,[1] the

[1] Archiv f. Gynäk. u. Obst., 1908, lxxxiv, 84.

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development of what is practically a new artery within the old, with endothelial, intimal, muscular, and even what corresponds to an adventitial coat. Here, we would hazard, the same principle is at work. The extreme congestion and dilatation of these arteries in menstruation and placentation leads to an overstrain of their walls with overexpansion and degenerative weakening of the same, to such an extent that at the conclusions of these physiological events, when there is no longer a call for dilatation of the arteries, they still remain expanded. Nor is there any adequate mechanism on the proximal side (toward the aorta) to cut off fully the blood supply. There is still, therefore, a certain amount of strain exerted upon the arterial walls from within, and this leads now to secondary overgrowth.

Secondly, Dr. Klotz has shown experimentally, and Saltykow[1] has confirmed, that certain bacterial toxins, *e. g.*, the diphtheritic, lead to medial degeneration, others, like typhoid toxins, have no recognizable effect upon this coat, but induce a primary intimal proliferation. I freely accept the existence of such primary intimal overgrowth. I have to confess, however, that I have some doubt as to its frequency as a cause of extensive arteriosclerosis in man. When it is at all well developed, then I would point out, the superficial intimal overgrowth cuts off the due nutrition of the musculo-elastic layer, and, indeed, of the innermost layer of the media; degeneration and weakening of these is the natural result, and there is established a vicious circle; the greater the intimal thickening the greater becomes the weakening of the lower intimal layer, and so of the arterial wall; nor is the full picture of arteriosclerosis attained until both events are present.

The same picture is afforded in the arterioles. My late colleague, Dr. Duval,[2] now professor of pathology at Tulane University, then pathologist to the Montreal General Hospital, published certain most interesting studies upon the effects of attenuated glanders bacilli upon the vascular system of the rabbit. In these he demonstrated most clearly that these bacilli induce an active proliferation of the endothelium of the smaller arteries, and he gives a figure of

[1] Ziegler's Beiträge, 1908, xlii, 187.

[2] Journal Experimental Medicine, 1907, ix, 241.

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a later stage in which a well-marked sclerotic node of the intima has associated with it a bulging and thinning of the media. If these two pictures represent successive phases of one process—and of that I am not wholly convinced—it must still be admitted that medial weakening, whether by the direct action of the glanders toxin or by arrest of nourishment of the media through the intimal hypertrophy, is an essential part of the process. Endothelial proliferation alone does not constitute arteriosclerosis.

Lastly, and perhaps of the greatest present importance, there is the consideration of the part played by the deeper or musculo-elastic layer of the aortic intima in the arteriosclerotic process. Following the lead of Jores,[1] the majority of the recent German writers on the subject lay stress upon the degeneration and hypertrophic processes found in this as being the fundamental change in arteriosclerosis. Here I have an objection to make of the same order as my criticism of the use of the term atherosclerosis, namely, that aortic disturbances are dwelt upon to the exclusion of the concomitant changes in the arteries of muscular type.

It is only in the larger branches of the aorta—those of the intermediate type—that this layer continues to be a factor of any importance. As we pass into the smaller arteries its development becomes so slight that it cannot possibly be a factor of the firs order.

In the aorta its fully developed structure—of longitudinally arranged plain muscle fibers and abundant elastic fibrillæ—renders it akin to the media. At most, the longitudinal arrangement of its elements suggests that its function is to oppose elongation rather than dilatation of the vessels in which it is present. Simple hypertrophy must connote increased strength of the arterial wall; degeneration of the same must signify weakening of the wall as a whole. Now, significantly this layer is curiously apt to exhibit degeneration. Why this should be so is not wholly understood. I would suggest that its position relative to sources of nutrition is largely at fault. The internal elastic lamellæ of the media largely cut it off from nutrition from without; the plasma from the interior of the vessel has to pass through and be acted upon by the more superficial layers of the

[1] Ziegler's Beiträge, 1902, xxxii, 146.

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intima before reaching it. It has no independent source of nutrition, and more particularly if the superficial layers of the intima have undergone thickening, the factors favoring degeneration are clearly greatly increased. The striking picture that this layer presents in the earlier stages of degeneration—the swollen condition of its cell elements, the edema of its interstitial substances, the diffuse soapy and fatty change that it undergoes—all, I am inclined to lay down, tend to arrest the attention and tend thus to a neglect of the concomitant medial and superficial intimal changes. And this point of view is supported by the existence of degenerative changes in the layer unaccompanied by any other vascular disturbance. In cases of burns and of acute infections, and that even in the young, it is common to meet with fine fatty streaks in the aorta. And these streaks indicate a fatty degeneration of, in the main, this musculo-elastic layer. It is natural to imagine that here we have the first stage in the arteriosclerotic process. I am, however, convinced that the two have no necessary association. I would ask anyone who doubts this to follow the example of Drs. J. McCrae and Klotz in our service at the Royal Victoria Hospital, and make a note upon the postmortem report every time that these fatty streaks are present. It will surprise him to find how common they are; how frequently they are present in the quite young; how little obvious relationship they have to the arteriosclerotic state.

I do not deny that a weakening of the musculo-elastic layer weakens the whole arterial wall, and thus may be a factor favoring subsequent intimal hypertrophy. I only urge that this is not nearly so frequent or so important as is a weakening of the media.

Thus we revert to our main conclusions that the dominant primary event in the arteriosclerotic process—syphilitic, senile, or functional—is a localized or it may be a diffuse weakening of the arterial wall and especially of the media. This induces increased strain upon the remaining coats; and if this be not excessive, that strain leads more especially to connective tissue overgrowth and the development of the characteristic lesions of arteriosclerosis.

In the foregoing remarks I have repeatedly referred to the work accomplished in our Montreal laboratories, and more particularly

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to the studies of Dr. Klotz. When the chief of a laboratory quotes the work of those under him, it is usual to infer that the work is his under another name—that he has inspired the researches. In justice to my colleague, I may say that in this instance this most decidedly is not the case. I have quoted Dr. Klotz's work so frequently because I have followed it with very deep interest and know intimately its progressive developments, and further because each step has, to my mind, confirmed and expanded the conclusions I reached long years ago regarding the essential nature of the arteriosclerotic process. I appreciate too highly the originality of Dr. Klotz to claim more than having been fortunate in suggesting to him that line of inquiry into the nature of calcification which he carried out with so much distinction and of which much of his later work is, as it were, a natural evolution. I should be glad to regard this address, and to have this address regarded, essentially as a vehicle for bringing forward in a connected manner the observations of my colleague and my interpretation of them, which must not necessarily be thought to be his interpretation.

Tuberculosis of the Aorta, and its Relation to Acute Miliary Tuberculosis.

By E. B. KRUMBHAAR, M.D.

The chief interest attaching to tuberculosis of the aorta or the larger bloodvessels is its causative relation to generalized or acute miliary tuberculosis. The credit for the first recognition of the latter condition must be given to Buhl,[1] who in 1856, many years before Koch's discovery of the tubercle bacillus, showed acute miliary tuberculosis to be a general disease (I quote his own words), "dependent on the former presence of an unencapsulated yellow tubercle, or a cavity in the lung, and has the same relation to the original focus as pyemia has to the original focus of suppuration." To be sure, Astley Cooper[2] had, in 1798, accurately described tuberculosis of the thoracic duct, and later, Ponfick[3] showed the connection between

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it and acute miliary tuberculosis, but they failed to draw the now well-accepted deduction that the thoracic duct is an important factor in the causation of acute miliary tuberculosis.

Interesting early cases of bloodvessel tubercles associated with acute miliary tuberculosis were reported by Lueken[4] in 1865 and Klebs[5] in 1876. The former found a tuberculous myocarditis rupturing into both ventricles, the latter a typical polypoid tubercle of the azygos vein. It was Weigert,[6] however, who emphasized the importance of tubercles of bloodvessels as the most frequent cause, and he should be considered the author of the present theory of the pathogenesis of miliary tuberculosis. His five postulates must be carefully considered in the study of these cases. They are: (1) The original tubercle must prove to be older than the acute miliary tubercles; (2) the tubercle must develop in an open vessel, *i. e.*, one that is not obliterated; (3) the tuberculous eruption must be of such a character as to allow a rich entrance of the poison into the blood; (4) the poison must actually reach the surface of the focus; (5) the tubercle must not be in any of the branches of the portal system, as in that case the liver will hold back most of the poison. He distinguished three kinds of hematogenous tuberculous infection, which classification is, in the main, still followed, though many intermediate forms also occur. They are: (1) An acute general miliary tuberculosis, with enormous numbers of minute gray tubercles throughout the system; (2) an intermediate form of generalized tuberculosis, consisting of a small number of tubercles in one or more organs, miliary or of different sizes; (3) a chronic generalized tuberculosis, consisting of widespread tuberculous foci in more chronic form. The last form may be aggravated by a supervening miliary tuberculosis, and it is to this class that the present case belongs. To this class also belong the cases of Ströbe,[7] Flexner,[8] Aschoff,[9] Longcope,[10] Schmorl,[11] Benda,[12] Blumer,[13] and the first of Simnitzky,[14] so that it is evidently a common form. Tubercles of the aorta, as part of a chronic general tuberculosis, without any miliary exacerbation, are apparently much rarer. I could only find two such cases in the literature (Lucksch[15] and Geissler[16]).

SUMMARY OF CASE. Extracts from the autopsy protocol (performed by Dr. W. T. Longcope, July 24, 1906, five hours after death)

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are as follows: William McA., aged forty years, white, clerk. Poorly developed, somewhat emaciated. Anatomical diagnosis: chronic diffuse peribronchial tuberculosis; chronic tuberculosis of intestines, kidneys, right testicle, seminal vesicles, prostate, and aorta; poliencephalitis superior; cloudy swelling of myocardium and kidneys. Microscopically, there were also found miliary tubercles of the liver, lungs, spleen, and intestines, and chronic passive congestion of the liver in addition to the lesions above described.

The aorta is smooth. About 3 cm. below the exit of the left subclavian artery there is a small, whitish, circumscribed raised nodule, about 3 mm. in diameter. It is raised at least 2 mm. above the surface, and has a finely granular surface. The iliac vessels are free from thrombi.

The thoracic duct has a rather smooth, but thick wall. No tubercles were found in it.

Sections, from the nodule on the aorta, were put through the routine fixation in Zenker's fluid, hardened in alcohol, embedded in paraffin, and stained in hematoxylin and eosin, Mallory's and Von Giesen's connective tissue stains, Weigert's stain for fibrin and bacteria in tissues, and Verhoeff's elastic tissue stain.

Microscopic examination showed the tuberculous process to involve all three coats of the artery, but chiefly the intima. The nodule on the intima is composed chiefly of reticulated, fibrinous and granular caseous material, staining reddish purple with hematoxylin and eosin, orange-yellow with a central cone of reddish purple with Mallory's counterstained with acid fuchsin. Surrounding this degenerating centre is a thick layer of coarse connective tissue, comparatively rich in cells, and with relatively few epithelioid cells. On the deeper edge of this layer are two beautiful multinuclear giant cells, with nuclei arranged about the periphery. The endothelial lining covers only a small part of the nuclei, and one part of its surface—presumably the half away from the heart—is covered by a fairly thick layer of fibrin (blue reticulum by Wright's stain) and detritus, which encloses some polymorphonuclear leukocytes and small round cells. The intima of the vessel wall is normal, but gradually thickens as it approaches the nodule.

The media (whose elastic fibers are beautifully depicted by

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Verhoeff's stain) is found to bulge immediately beneath the nodule to enclose a small sphere of connective tissue with a necrotic area in its centre, similar to that described in the intima. Adjacent to this the elastic fibers are separated, thinned out, and in many cases ruptured and curled up. This passes through the deeper layer of the split media by a well-defined band of similar connective tissue to join the adventitia. No connection is found with the intima in the several sections examined, but in the absence of serial sections this point cannot be decided; though in all probability such connection did exist. Epithelioid and rather atypical giant cells are also found here, but no tubercle bacilli. The adventitia is also thickened beneath the nodule. The loose areolar tissue is replaced by a denser connective tissue, rich in bloodvessels, and in one place there is a large collection of red blood cells, free in the tissue. In the deepest layers the loose areolar arrangement is comparatively normal.

A few millimeters from the above nodule is a place where the intima is puckered. The media, below this, is thinned and sends some elastic fibers well into the underlying adventitia. This is probably part of a small branch of the aorta, but might possibly be a minute aneurysm following a former tuberculous focus. This also cannot be decided in the absence of serial sections. No tubercle bacilli were found in any of the sections examined. (N. B.—The length of time between the death of the patient and the preparation of the tissue—over two years—may have contributed to this failure.)

The sequence of events seems to have been, in this case, that during the course of a chronic generalized tuberculosis a solitary tubercle was formed on the intima of the aorta, following the deposition of tubercle bacilli from the blood stream. This attained considerable size, and went on to caseation. Shortly before death a considerable number of tubercle bacilli were liberated in the blood stream, presumably from this tubercle, causing a miliary crop in the liver, spleen, and intestines. Whether or not the miliary tubercles were formed by an invasion of the blood stream by bacilli from this tubercle, especially in the absence of tubercle bacilli, cannot be determined. In the sections examined, the caseous portion was fairly well walled off, but the small thrombus might easily have formed a base, or perhaps in other sections the bacillus-containing portions were

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nearer the surface. The character of the histological changes and the fact that no gross tuberculous lesion is noted in the neighborhood make it reasonably certain that the process in the intima was the primary one.

Weigert's theory has met with certain objections, some of them well founded, so that the pathogenesis of miliary tuberculosis is still far from settled. For instance, he laid particular stress on the fact that the vessel tubercle was usually secondary to some neighboring focus, the process extending into the vessel wall by contiguity. Benda and others, however, have demonstrated, as in the present case, that the vessel tubercle usually occurs from metastasis by the blood stream. Ribbert[17] and his pupil Wild[18] renounce the whole Weigert theory as the explanation of the majority of cases, and consider that in most cases the miliary tuberculosis is caused by the active proliferation of the bacilli in the blood stream, after they have broken in by devious ways and in insufficient quantities. His objections to Weigert's theory are, that there are many cases in which no large vessel focus is found; that if the focus is present, it is often not rich enough in bacilli to account for the number of miliary tubercles found; that the vessel focus is often found not ulcerated; that the different sizes of the miliary tubercles presume a difference in age. In refutation of this, Weigert has found adequate vessel tubercles in 70.8 per cent. of cases of miliary tuberculosis, Schmorl in 95 per cent., and more recently Silbergleit[19] in 95 per cent. of 23 cases. Eleven of these were in pulmonary veins and five in the thoracic duct. A more important objection is the observation of Baumgarten[20] that in experimental tuberculosis the animals succumb to an acute miliary tuberculosis without the production of tubercles of the larger vessels, but in this case the conditions are far from natural, and it may easily be that instead of a true miliary tuberculosis in Weigert's and Benda's sense, a more virulent form of chronic generalized tuberculosis is formed.

If tubercle bacilli are disseminated through the body by the blood stream, the question naturally arises why tubercles of the intima, so long as they are occasionally found, are not found more frequently. A predisposing cause which sufficiently lowers the resistance of a given area is sought for, and arteriosclerosis at once suggests itself.

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But, unfortunately, arteriosclerosis not only occurs in too many cases of tuberculosis without tubercles of the larger vessels, but also a fair percentage of cases of tuberculosis of the aorta show no arteriosclerosis (Longcope,[10] Ströbe,[7] and the present case). The action of toxins, either those elaborated by the tubercle bacilli or from any other external or internal cause, has also been suggested, but no evidence has been offered in support of this theory, so that at present the question must remain unanswered.

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April 8, 1909.

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Card Specimens Presented May 27, 1909.

DR. HARLAN SHOEMAKER FOR DR. J. M. HAMMOND:

Two Specimens of Carcinoma of the Fundus Uteri.

The point of interest in these two specimens lies in the fact that at the junction of the invading cancer and the uterine musculature a very sharp demarcation is noted. The uterine muscle is being rapidly changed to fibromyomata. Innumerable fibroid whirls are seen in the sections, while in the gross specimen the uterine body is thicker and firmer than that usually observed. The parasitic nature of the growth is suggested by the appearance of the nests of carcinomatous cells flattened against the fibroid uterine muscle.

DR. W. T. LONGCOPE AND DR. E. B. KRUMBHAAR

A Series of Tumors of the Liver.

These five tumors of the liver, found at autopsy at the Pennsylvania Hospital during the last six months, may be grouped in an interesting progression. The first is a simple adenoma; the second, occurring in a cirrhotic liver with widespread areas of regeneration, represents probably a malignant change of these areas with secondary metastases through the left lobe; the third is a primary adenocarcinoma arising from the liver cells; the fourth, a primary carcinoma arising from the intrahepatic bile ducts; the fifth, an endothelioma of the branches of the portal vein.

In more detail, the specimen of simple adenoma occurred in a small terrier, a pet dog in my family for many years. He died at the advanced age of sixteen, after having become much emaciated and weakened. At autopsy the liver was found to consist of several distinct lobes, and this tumor occupied almost all of the largest one. Microscopically, it consists of much vacuolated liver cells, surrounded by many vessels and not showing any lobular arrangement, portal spaces, or bile ducts. Except for these characteristics it is difficult to distinguish it from the liver tissue.

The second specimen shows a marked cirrhosis in one lobe, with

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numerous nodules of regeneration. The other lobe is mostly filled with secondary nodules, and, as no primary carcinoma was found elsewhere in the body, it is most probable that the regenerating areas had taken on the characteristics of a malignant tumor with metastases to the other lobe and neighboring lymph nodes, and emboli in the pulmonary artery.

The primary adenocarcinoma arising from the liver cells was found at autopsy by Dr. Longcope in a Chinaman. It belongs to the alveolar type, with many nodules, as opposed to both the infiltrating type and the cancer massif of Hanot. Microscopically, fairly well-circumscribed nodules of cells, closely resembling liver cells, are found scattered through the section. Mitotic figures are numerous. The nodules are not umbilicated, as is often the case in secondary nodules.

The primary carcinoma of the bile duct is more of the infiltrating type. Microscopically, new-forming atypical bile ducts, with numerous mitotic figures, are well shown on the edge of the tumor. The centre is entirely necrotic. The liver is also cirrhotic in this case. Metastasis occurred to the pleura, peritoneum, and lymph nodes of various regions.

The last case, in which Dr. Longcope performed the autopsy, was diagnosticated by him as an endothelioma of the portal vein. Both it and the hepatic duct were occluded by the newgrowth, which grew into the finest radicals of the vein and seemed firmly attached to the wall.

DR. JAMES M. ANDERS:

A Solitary Kidney Showing Chronic Interstitial Nephritis.

This specimen was taken from a male subject, aged sixty-four years, an Englishman, who was admitted to the Medico-Chirurgical Hospital April 10, suffering from chronic interstitial nephritis. He died two weeks later from bronchopneumonia. In an autopsy made a few hours later the lungs presented the lesions of bronchial pneumonia. On opening the abdominal cavity the left kidney, left suprarenal gland, left renal artery and vein, as well as the ureter of the same side, were missing. The existing kidney was distinctly

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enlarged and more or less lobulated. The right suprarenal gland was somewhat hypertrophied, as was also the right ureter. The pelvis of this existing kidney was proportionately enlarged, but with not the slightest indication of duplication. The right renal artery bifurcated just before entering the renal structure, and was also enlarged. The genitalia were apparently normal throughout. The examination of the existing kidney was made by Dr. Case, who reported the histological changes to be those of chronic interstitial nephritis with some parenchymatous change. It was apparent that the increase in size was due to the numerical increase of anatomical structures rather than to enlargement of the various tissue elements. This was not a case of urogenital aplasia, but a true case of unilateral urinary defect.

DR. DAVID RIESMAN AND DR. JOHN M. SWAN:

Two Specimens of Bothriocephalus Latus.

In December, 1901, I exhibited before the Society a specimen of Bothriocephalus latus from a Russian woman, the fourth case observed in Philadelphia. Since then a number of others have been reported in this city (McFarland, Willson, Edsall, A. J. Smith), and two more have come under my own observation. One of the worms shown tonight was obtained from a Roumanian girl, aged nineteen years, who first noticed the passings of links while dwelling in Paris, where she had then lived for about three years. She came to this country five years ago; I saw her two years ago as a dispensary patient, at the Polyclinic Hospital, but failed in bringing about the expulsion of the worm. Recently I had her again under treatment, and obtained five feet of worm, but not the head.

The second specimen, also headless, comes from a Russian woman, aged twenty-seven years, who has resided in the United States nine years, six of which were spent in Boston. She has had signs of the worm for five years.

Neither of the patients had any anemia; this was also true of the case reported in 1901.

The worms, one of which was carefully studied by Dr. Swan, present the characteristic features of the Dibothriocephalus latus described in detail in my first paper (*Medicine*, Detroit, February, 1902).

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DR. ALLEN J. SMITH:

Acid-fast Bacilli in Bile from a Tuberculous Cadaver; Tubercle Bacilli in Gallstones of a Guinea-pig Inoculated with Tubercle Bacilli.

Reasoning upon the basis of Dr. Rosenberger's report before this Society that in tuberculous patients a high proportion show the presence of tubercle bacilli in the blood, I have thought that following such bacillemia the tubercle bacilli should be demonstrable in the bile and have searched for the organisms in bile obtained at autopsy from a number of tuberculous patients. In several, acid-fast organisms, morphologically like tubercle bacilli, have been found, and a slide of such preparation is demonstrated containing numerous organisms of this type. The preparations were made by diluting the bile with a weak solution of potassium hydrate to dissolve the mucin in it, then precipitating by centrifuge and making a smear of the precipitate and staining as ordinarily for tubercle bacilli.

Lest there be objection that such organisms are not true tubercle bacilli, I prepared sections of the livers of guinea-pigs inoculated with bovine bacilli and having well-developed tuberculous lesions often in the liver as well as elsewhere in the body, and in a number of these I have found the organisms within the bile ducts of the sections. A section of this type is exhibited.

In view of these findings it may be thought credible that infection of the intestine may occur in tuberculous individuals through the biliary route in addition to infections arising from swallowing the tuberculous sputum.

Note upon Additional Cases of Blastomycosis.

BY ALLEN J. SMITH, M.D.

(From the McManes Laboratory of Pathology, University of Pennsylvania.)

SOME months since[1] the writer, in conjunction with Drs. Posey, Carpenter, and Hosmer, reported the occurrence of two cases of parasitic nodular conjunctivitis, in which there were found certain unusual

[1] University of Pennsylvania Medical Bulletin, November, 1908.

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forms of blastomycetoid organisms, which the writers regarded not as true forms of blastomycetes, but as reversionary forms (from parasitism) of some higher types of fungi.

In addition to these, two other instances of blastomycetic infection have been encountered in the work of the pathological laboratory, in both cases occurring in the skin as ulcerous and fungating sores.[1] Both of these cases were referred through the Laboratory of the State Health Department, the tissues fixed in formaldehyde solution for days or even for weeks. Attempts were made in each instance to procure fresh material for purposes of culture, but in spite of written requests, and the fact that the tissue in one instance was obtained from the person of a medical man, no responses could be gotten, and the specimens must, therefore, be reported merely for record of occurrence of the affection in this state.

In the general group of blastomycosis at least three types may be distinguished from the viewpoint of the form of organism encountered, viz., instances of true blastomycosis, examples of oidial infection with reversion of the oidium in its parasitic life in the tissues to a monocellular reproductive type of mould, and a third group of cases in which are found blastomycetoid forms which differ materially in mode of reproduction and in size from both of the former, and which are probably reversionary forms of higher fungi.

True blastomycetes are forms of fungi reproducing constantly or at times by gemmation, but not growing filaments and incapable of producing a true mycelium; and include the *saccharomycetes*, which have the power of fermenting sugars and of formation of endogenous ascospores, and also the *torulæ*, which, as a rule, are non-fermenting and do not form spores, but reproduce by gemmation.[2] Although at first cases of infection were held as probably or possibly protozoic in nature,[3] no actual verification of this supposition exists, and the organisms are generally accepted as of vegetable nature. As substantiating the second class above mentioned, it has been shown by

[1] Path. Hist., 1860 and 1648.

[2] Weis, Journal of Medical Research, April, 1902, viii, 280.

[3] *E. g.*, Wernicke's case, Centralbl. f. Bakt. u. Parasitenk., 1892, xii, 859; and that of Gilchrist and Rixford, Johns Hopkins Hospital Reports, 1896, No. 1, p. 209.

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culture methods[1] that a number of the organisms which in the tissues present the morphology of true blastomycetes are in reality oidia, which have probably reverted to independently producing single cells in their parasitic occurrence in the tissues, but which in artificial media form definite mycelia. The conjunctival cases reported by the writer and his associates (*sup. cit.*) and the cases of sporothrix infection[2] are illustrations in point to the view that other types of fungi of higher form (or possibly myxomycetes) may similarly in parasitic condition revert to blastomycetoid characters and constitute the third class above mentioned.

Of the two cases here reported, one presents the usual character of the organisms which have been described in most of the cases of blastomycosis; although without the chance for cultural studies it is impossible to say whether they are true blastomycetes or oidial reversions to blastomycetic character. The patient was a white male, American born, aged forty-five years, a miner, living in the interior of this State, with dermal lesions of some standing which were regarded as epitheliomatous. A single lesion fixed in formaldehyde solution was submitted for examination by his physician with no further description than this, and although repeatedly besought for fuller data and fresh material for culture, the physician neglected furnishing either. The lesion received was evidently a tuberous growth, with circular base about 2 cm. in diameter and an elevation of about 1 cm. to the rounded top. Sections show the base to be made up of the ordinary corium, with but minor inflammatory changes along the bloodvessels and gland ducts. The epidermal surface is considerably thickened, the proliferation involving especially the deeper prickle layers, and accompanied by the penetration of thick, irregularly branching, root-like extensions into the upper part of the corium. Occasional poorly formed concentric epithelial nests occur. In vacuoles in the epithelium, but in greater proportions and more diffusely in the corium surrounding the epidermal roots, there is to be noted a marked polynuclear leukocytic infiltration, occasionally con-

[1] Originally by Ophüls and Moffitt, Philadelphia Medical Journal, 1900, v, 1471, and subsequently by Ricketts, Journal of Medical Research, vi, 373, and by a number of other investigators.

[2] *E. g.*, that of Hektoen and Perkins, Journal of Experimental Medicine, 1900, v, 77.

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centrated in small suppurative foci; and in this part of the corium an active fibro-angioplastic process prevails. Numerous plasma cells and, too, occasional mast cells occur, together with a moderate eosinophilia. Karyokinetic nuclei are found both in the epithelium and in the connective-tissue cells of this upper part of the corium. Here and there are definite giant cells in the involved part of the corium, usually close to the epithelial roots, and the writer is of the impression, from their position and appearance, that they are, at least in part, of epithelial origin. For the most part the multiple nuclei of these cells are clumped in a central mass as in "foreign body giant cells," but some have the peripheral nuclear arrangement seen in the giant cells of tuberculosis. The blastomycetic organisms have not, after careful search throughout numerous sections of this material, been found in the giant cells, as is commonly reported, but are found usually in or about the minute suppurative foci above mentioned, occasionally well out in the fibroplastic stratum, closer to the normal corium. They vary slightly in size, but average 10 m.mm. in diameter, are spherical in shape, provided with a sharply defined, double contoured, refractile cell wall which takes the eosin tint, and with a granular hematoxylin staining protoplasm. No examples showing endogenous sporulation were met; but occasional budding and dumb-bell individuals were seen.

The second instance occurred in the person of a physician in the western part of Pennsylvania, white, male, aged fifty years. Symmetrical fungous ulceration occurred on the cheeks, described as of rapid development, from one of which a portion of tissue was sent to the laboratory for examination, already fixed. In section this includes numerous fibers of striated muscle from the cheek, and the loose overlying connective tissue; but the epiderm is missing, and no traces of epithelial growth have been found in the sections made from the material. Throughout the entire specimen there are evidences of tissue destruction and of new tissue formation. The deeper part of the muscle is relatively unchanged, but even here vacuolization and myolysis are apparent, and more superficially, in the loose, edematous tissue, fragments of muscle fiber occur where originally normal muscle must have prevailed. The general tissue is rich in embryonic connective-tissue cells and fibroblasts, and numerous vascular sprouts are

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seen penetrating the mass. The endothelium of the vessels and of lymph spaces is largely proliferating and swollen; and here and there throughout the more actively inflamed parts are endothelioid groups, suggesting the centres of tubercles. Nuclear multiplication and swelling of the fibers of muscle have led to the formation of numerous large "muscle giant cells," and among these are smaller ones, usually staining less deeply, which possibly may be of other origin. There is but little recognized leukocytic presence. The lesion is thus to be regarded as originally necrosing, destroying the skin and superficial structures and reaching well down to the muscle, but at the stage obtained in the material submitted showing active organization and repair. Scattered in sparse numbers throughout the cellular areas, but here and there collected in special minute foci, are encountered cellular bodies of about the same size as polynuclear leukocytes, which the writer believes to be a type of blastomyces, smaller than the ordinary forms described and staining differentially both from the ordinary blastomycetes and also from the body cells with special methods. They are round to oval in shape, and numerous dumb-bell forms occur. With hematoxylin and eosin the wall shows as a thick, single, deeply blue outline, the interior taking a lighter blue tint and showing several (2–3–4) vacuoles (suggesting endogenous spores of yeasts); no nucleus has been recognized. With Gram's stain these bodies are positive, and in carbolfuchsin and methylene blue preparation they retain the fuchsin. No cellulose reaction could, however, be brought out in the sections. No mycelial filaments have been seen; and no bacteria of any type have been recognized in the special preparations. Without the information which might have been obtained from cultural or inoculation studies it is impossible to be entirely sure of these organisms. They distinctly differ in size and in mode of staining from the common blastomycetes thus far described. That they are not, as has been suggested, nuclei of lymphocytes or other cells of the body seems indicated by the distinctive staining with special stains, the sharp outline indicating absence of protoplasm about them, the occurrence of what seem to be budding forms, and the common interior vacuoles. Further, while most of these bodies are uniform in size, there occur numbers of smaller ones having the same structural and tinctorial peculiarities. In response to requests for fresh material for culture

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purposes, the writer was told this would be done when the patient should return from a vacation trip; but after several months further information was received that the lesions upon both cheeks had disappeared during this trip. The short course of the case, its favorable termination, and the absence of epithelial proliferation and of suppuration mark it as differing essentially in clinical character from ordinary blastomycosis. The writer is disposed to believe it an infection by some unusual type of yeast, but must leave the actual determination open to future encounter with similar bodies under circumstances permitting fuller study.

Colloids.

By HENRY LEFFMANN.[1]

It was in 1861 that the eminent English chemist Thomas Graham gave to the word "colloid" its special significance in physical chemistry. Upon the deportment of substances in relation to specific conditions of diffusion he based a classification into "crystalloid" and "colloid." Solutions of the former substances pass readily through membranes, especially parchment paper; solutions of the latter pass slowly or not at all. He pointed out that practical applications could be made of these differences, just as similar applications are made of differences in solubility and volatility. Indeed, it was not long after the publication of these investigations that it was suggested to use the principle in separating the crystalloid arsenous oxide from the colloid substances with which it is usually mixed in the materials submitted to toxicological analysis.

Nevertheless, Graham's researches did not attract the attention that we now know they deserve. Investigation has been going on, and by the invention of new methods of observation interesting and important facts have been brought to light. I am old enough to remember the publication of Graham's first work, having, indeed, begun the study of chemistry in that year. At the present time the

[1] By invitation.

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literature on colloids is voluminous, and a special journal is devoted to the subject—of course, a German journal, the *Zeitschrift für die Chemie und Industrie der Kolloïde.*

It is but fair that I should confess that having not devoted any part of my active work in the laboratory to the colloids, I am compelled to draw the material for this paper from the literature, and I am indebted especially to three sources—a paper on "Colloidal Mixtures," by A. A. Noyes, published in the *Journal of the American Chemical Society*, in 1905; a recent work by W. M. Bayliss, on *The Chemical and Physical Properties of Enzymes*, in which a chapter on the "Nature of Enzyme Action" gives much recent information; and Zsigmondy's book *Die Kolloïde.*

It appears from the literature that the term colloid has undergone some change in scope since Graham's day. In its earlier use, the idea of viscosity, or distinct jelly-like condition, was prominent, and such substances as gelatin, albumin, and the mucilages were typical examples. Not much suggestion was offered as to the nature of the mass when the colloid "jells," as the common expression goes, but, doubtless, the general impression was that the solid separated completely but remained in close contact with the liquid, assuming no definite geometric form, thus constituting an essential difference from crystalloids. It must be borne in mind that the distinction between these two classes is not an absolute one, since many substances can assume either form. It is true that a crystalline form has been produced with but few organic colloids, but many mineral substances afford instances of convertibility. Thus, silicon dioxide, which, in flint and several allied forms is colloidal, shows in quartz the highest type of crystalline structure; indeed, this is the mineral from which the word "crystal" is derived.

In modern literature the term colloid has been extended so as to include conditions that would have been regarded as mere physical suspensions in the earlier period. Noyes, to whose article I have already referred, lays more stress on this distinction than most writers, and, I think, justly, pointing out that there is a great deal of physical and chemical difference between the highly viscous solutions produced by gelatin, agar, and similar organic bodies and the non-viscous liquids that are observed in the so-called colloidal metals

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or compounds. Another point of distinction must also be noted. Such colloids as gelatin and agar, for instance, are not precipitated by the addition of ordinary salts, unless, perhaps, when added in very large amounts, they act as dehydrating agents, but the colloidal suspensions of the metals or of inorganic compounds are thrown down by small amounts of salts or acids. Speaking generally, the precipitation occurs when electrolytes are added, that is, substances which are capable of conducting electricity and being decomposed by it; in brief, bodies which ionize readily. It has been determined, indeed, that colloids are capable of assuming electrical charges, and, in fact, do often assume such charge. The essential difference between this condition and that which prevails with ordinary ions is that while, with the latter, the charge assumed is always the same in nature and amount for any given ion, the colloid masses do not show constancy in these respects. Arsenous sulphide prepared by the action of hydrogen sulphide upon arsenous acid in water has a negative charge; ferric hydroxide, prepared by the dialysis of ferric chloride solution, has a positive charge. Serum globulin in neutral solution has no charge; by the action of acid it assumes a positive charge, by the action of alkali a negative one. In this latter example it may be assumed, with good reason, that hydrions or hydroxions are taken up as the case may be. The existence of electrical charges upon colloidal suspensions can be determined by passing a current through the suspension; the colloid will then move toward the pole of opposite name.

In a paper of the limits of this it will be possible only to present some of the data; the more recondite points, such as osmotic pressure and these electrical relations, cannot be fully discussed. A step of considerable importance in the study of the colloids was taken when Zsigmondy and Siedentopf devised the "ultra microscope," enabling the observation of particles much too minute for ordinary instruments. By this it has been found that many liquids contain suspensions, though they appear to ordinary vision as solutions. In all attempts at classification and definition, we meet with intermediate conditions that embarrass us. We find no difficulty in distinguishing between animals and plants when we compare a sparrow with a hyacinth, nor any difficulty in distinguishing a solution from a sus-

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pension when we compare simple syrup with milk, but between the extremes in each of these cases is a long line of intermediates passing insensibly from one into the other, so that we can delimit only by arbitrary judgment. We place the sparrow and the hyacinth in their respective classes without hesitation or dispute, but what shall we do with the slime moulds? Everyone will consider simple syrup as a solution and milk as a suspension, but how shall we classify starch jelly? Is brass a mixture or a compound of copper and zinc? In the class that Noyes terms "colloidal solutions" several of the striking physical characters are those of true solutions. The important point distinguishing the condition, usually designated suspension, from the true colloidal state is the size of the particles. Before describing these conditions, a few preliminary explanations are necessary. Everyone knows that the more finely we powder a solid the more easily we can suspend it in a liquid in which it is insoluble and maintain it thus. It is true that several conditions affect this suspension, but other things being equal, the finest powder will remain suspended the longest. This is the basis of the well-known process of elutriation, applied in the manufacture of prepared chalk and in the grading of grinding powders.

Now by chemical means we can often obtain much finer division than by mechanical means. Quevenne's iron is an example of the use of indirect chemical means by which we get a fineness far beyond that of the finest filings. If, however, we bring about reactions between substances in dilute solution or in vapor, the degree of division is often very minute, and some of the common physical properties of the resulting body are much modified. Thus, if I make a mixture of mercuric chloride and stannous chloride, the latter takes all the chlorine from the former and the mercury separates as an impalpable powder which, though the metal is thirteen and a half times as heavy as water, remains suspended for a long while and does not resemble ordinary mercury. This shows, too, the important point that the characteristic lustre and fluidity of mercury are not inherent properties of its atoms, but are manifestations of the particular state of aggregation of the atoms which we ordinarily see. Gold, silver, and platinum can easily be obtained in a similar condition. Of late years, however, the degree of division has been carried

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much farther and liquids produced that appear to ordinary vision to be solutions, being clear, though highly colored. By the application of the "ultra microscope" the nature of these liquids has been elucidated. The investigation has depended very largely upon the observation of what is known as Faraday-Tyndall effect. This is obtained by passing a powerful beam of light through the liquid. If particles in suspension are present, the path of the beam becomes visible as a bright streak when viewed from the side. This is the same principle by which we follow the course of the sunbeam through the dust of our living rooms. In the case of colloidal solutions that do not deposit on standing, the light sent out at right angles to the path of the beam is polarized; this fact, the physicist tells us, shows that the reflecting particles are smaller than the mean wave-length of the light forming the beam.

It will also be easily understood that in proportion as a mass is broken up its surface is increased. Assume a cube one inch on the side; this will have a surface of six square inches. If we cut the cube by planes parallel to any side, the total surface will be eight square inches. According to Zsigmondy and Siedentopf (quoted by Bayliss), certain colloidal gold suspensions contain particles with a radius of 0.00001 mm. A sphere of 1 mm. radius, if divided into spheres of 0.00001 mm. radius, would have a total surface of 100 sq. meters.

Colloidal suspension must, therefore, exhibit enormous development of surface. In tracing out the inferences and results from this condition, we come to some very abstruse questions in physical chemistry. I fear I can do little to elucidate them. It might be supposed that if we continued the division of particles and finally reached a separation into individual molecules, which is the limit of physical divisibility of any substance, that we would then get the highest surface action, but it is held by many that while individual molecules occupy space and, therefore, have the three dimensions which are always associated with occupancy, yet they do not have limiting surfaces such as are exhibited by true mass. It has been suggested that true solution is a separation into individual molecules, while suspensions are separations into masses of few or many molecules, according as the suspended particles are smaller or larger.

One of the most important physical properties dependent on

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extension of surface is increase of surface tension. When solids are immersed in liquids in which they do not dissolve, the surfaces of contact between the liquid and the solid act as if stretched. Any free surface of a liquid, which is, of course, in contact with atmosphere, shows this condition. Now, it has been shown by mathematical reasoning that if a liquid contains anything in solution that tends to reduce surface tension, and most soluble bodies do this, the reduction of the surface tension will take place where the liquid is in contact with the suspended particles. As in these so-called colloidal suspensions, the division of particles has been carried very far, the opportunities for such surface action are very great, hence phenomena of association occur abundantly and colloids show great power of attracting other substances, even those in solution. This phenomenon is termed "adsorption." Many instances of this action are known. The action of aluminum hydroxide in withdrawing suspended and dissolved matters from water is an example; also the action of ferric hydroxide in withdrawing arsenous oxide from its solution. This latter action, upon which depends the antidotal value of ferric hydroxide in arsenic poisoning, was formerly thought to be wholly chemical (the formation of ferrous arsenate) but is mainly a physical action.

Enzymes show striking colloidal conditions. They pass very slowly or not at all through parchment paper. They will, therefore, show strongly the phenomenon of adsorption. The constituents of protoplasm are mostly colloidal, and the substances dissolved in the fluids of the cells are mostly in dilute solution.

The attraction between two colloids will be developed by the inherent power of the surface tension, but it will be materially aided if the two receive electrical charges of opposite sign. These "adsorption compounds," or "colloid complexes," as they have been termed, play an important part in physiological chemistry, but a striking illustration is drawn from inorganic chemistry. When electronegative arsenous sulphide is mixed with electropositive ferric hydroxide in such proportions that the resulting mixture is neutral, both bodies are thrown down and the liquid becomes clear. These so-called compounds differ from those with which the chemist ordinarily deals in that the latter are definite in their constitution, while the proportion

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of constituents in the colloid complexes is dependent on the relative proportion of the formative bodies in the solutions. Bayliss gives the following illustrations of the differences between solution, colloidal combination, and chemical combination. Picric acid is soluble in water and ether, but is more soluble in the latter.

With a given mixture of ether, water, and picric acid, a given amount of the acid will pass into the water and a still larger part into the ether. Now, if the quantity of the acid is doubled, such liquid will double its quota, and the relative proportions dissolved in the respective liquids will remain the same. If to a definite quantity of silver nitrate, a given amount of sodium chloride is added, all the silver is converted into chloride, and the further addition of chloride produces no effect. In fact, it makes no difference in what proportion we mix the two substances. One or the other is completely decomposed and the product is always the same. This law of constant proportion is one of the most important principles of chemistry, and largely contributes to making it an exact science. As an example of a colloid complex Bayliss takes filter paper with congo red. Filter paper dipped into congo red solution withdraws the color, but not all of it. If the amount in the solution is doubled, more is taken up, but not the double amount; somewhat less. Thus the formation of the colloidal complex differs from both true physical action and true chemical action. It does not follow the strict ratio of either. It will be seen by this that a relatively larger proportion of the colloid reacts when the solution is dilute. This general rule has an important bearing upon many physiological phenomena.

Enzymes, as I have already stated, are colloids and have the power of carrying down with them by adsorption substances in solution. This is one of the causes of the difficulty in getting enzymes in the pure state.

It is apparent, then, that the known facts in regard to colloidal conditions constitute a field which would be correctly described by using the phrase which Mr. Pickwick gave Count Smaltork as a definition of politics—"a difficult study of no inconsiderable magnitude." The difficulties have been increased by the undue extension of the term, and it is to be hoped that Noyes' suggestion will be adopted and the word *colloid*, at least, limited to conditions which

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are closely allied to those presented by the bodies that Graham studied. The preparations of gold, silver, arsenous sulphide, ferric hydroxide are not sufficiently similar to those of a gelatin, agar, Iceland moss, and other well known organic bodies to justify inclusion under one specific term.

Discussion.

Dr. William H. Welker: The rapid advances made in physical chemistry during the last twenty-five years have been of great value to the medical profession and to physiological chemistry. Colloids in solution, as we have been told by Dr. Leffmann, have very little or no osmotic pressure, and are not diffusible. These properties allow of their storage in the cells of living plants or animals without causing osmotic or other disturbances.

In nature, then, to handle a substance in the sap of a plant or in the blood of an animal, it would seem desirable that it should be in the form of a diffusible substance. These substances are known as crystalloids. When it is stored in the cell, the substance should again be converted into a colloidal or non-diffusible compound. The most familiar example of this is the way carbohydrates are handled in plants. The plants are supposed to form glucose from carbon dioxide and water. This enters the sap and as a diffusible substance it is carried to the tissues and is stored as the non-diffusible substance, starch. This conversion removes the carbohydrate from the active chemical field, and it remains inert unless it becomes hydrolyzed into a carbohydrate, that is, of the crystalloid type.

In the animal organism the glucose as an end product of carbohydrate digestion is absorbed into the blood and is stored mainly in the liver as the animal starch, glycogen. There it remains inert until needed in the blood, when it takes on the crystalloid form of glucose.

The situation with the proteins in the animal organism is somewhat similar, but it is a little more complicated. In the main, protein material injected remains colloidal until the enzymes of the pancreatic juice act on it, when it is converted into crystalloid material. It reaches the blood again in the form of colloid. In some work that was carried out in the Laboratory of Biological Chemistry at Columbia

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University by several others and myself, it was found that salts of proteins, particularly mucoid compounds with potassium, sodium, calcium, and barium, were diffusible to quite an extent. Also that their solutions exerted some osmotic pressure and that some dissociation occurred in these solutions. This property of diffusibility was studied by others in the same laboratory in connection with salts of various other proteins, and it was found common to practically all of them.

Assuming that a protein salt of some of the serum albumin is formed in the blood, it is easy to see how this then could diffuse into the cells, and on account of its dissociation readily react with other compounds and become changed again to colloidal material, and held there as such and subsequently modified to the individual needs of the cell.

Another very important consideration is the fact that the enzymes, as a rule, are colloidal in character. This property of enzymes explains how these bodies are held within the respective cell walls, and also how a single cell may have in its various parts different enzymes carrying out diametrically opposite chemical processes.

The size of the molecule was at one time supposed to have a great bearing on the question of whether a substance belonged to the colloids or crystalloids. From the observations previously stated, it would seem that the size of the molecule had no particular bearing on the question, for if the protein molecule can be changed from a colloidal to a crystalloid substance by the mere addition of a few sodium atoms, no simplification of the molecule seems to be involved.

Attempts have been made to explain the nature of nerve impulse and muscle contraction on the basis of change of state in the colloidal materials present. Up to the present time, however, the theories seem to have rather large loopholes.

From the preceding illustrations, it can be readily seen how much aid medicine and physiological chemistry have received toward explaining some of the phenomena that occur in the living organism. There is, however, a tremendous field for investigation, and the physiological chemists are turning their attention in this direction. I feel confident in saying that the results of their efforts will bring us to a fuller understanding of some of the obscure problems.

May 27, 1909.

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Compression of the Pulmonary Veins the Pressure Factor in the Etiology of Cardiac Hydrothorax.

By GEORGE FETTEROLF, A.B., M.D., and H. R. M. LANDIS, A.B., M.D.

(From the Laboratory of Anatomy of the University of Pennsylvania and the Jefferson Medical College Hospital.)

The hydrothorax that sometimes accompanies heart disease has been recognized for many years. Why it occurs in some cases and not in others is not clear, for it is certain, as both Flint and Da Costa[1] long since remarked, that the phenomenon bears no constant relation to the extent of the cardiac disease. "Not only are these lesions (cardiac) marked in cases in which dropsy has not occurred, but dropsy occurs in other cases in which the lesions are comparatively slight" (Flint[2]).

In seeking an adequate explanation for the occurrence of these effusions we have concerned ourselves chiefly with the effects, the mechanical effects, arising from pressure exerted by the dilated heart. We recognize fully that before an effusion can occur the presence of factors other than pressure may be necessary, for example, toxic, vasomotor, bacterial, or metabolic influences, or a hydremic condition of the blood. Krehl[3] states in this connection: "Certain patients suffering from heart disease in the state of broken compensation show a watery condition of the blood, both the specific gravity and the proportion of proteids in the blood being diminished (Grawitz). A weakness of the right ventricle is especially apt to give rise to such a thing in the blood. . . . This hydremia occurs in a comparatively small proportion of all cases of broken compensation; but where it does occur it is quite usual for it to disappear with any improvement in the circulation."

Any one of those agents, however, which affect the composition of the blood will fail to account for the fact that these effusions have a marked preference for one or the other side of the chest, usually the right. That pressure alone will cause the transudate is improb-

[1] Medical Diagnosis, eighth edition, p. 422.

[2] Diseases of the Heart, second edition, 1870, p. 37.

[3] Clinical Pathology, American edition, 1905, p. 176.

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able, but it is certainly a factor of the greatest importance. Another point is that the pressure must be from dilatation, as it has long been recognized that hypertrophy of the heart by itself is incapable of producing an effusion, and that dilatation, with or without valvular lesions, is an essential feature.

Recognizing that dilatation of the heart was necessary, most observers contented themselves with the explanation that a transudation resulted from venous stasis, either alone or in association with impoverishment of the blood. In recent years, however, the azygos-vein theory has been much in favor, largely as a result of papers published by Steele[1] and Stengel.[2] Their explanation of these effusions, and particularly of the right-sided preponderance, is that the dilated right heart by extension upward exerts pressure on the root of the right lung and thus indirectly pinches the azygos major vein as it curves over the root of the right lung to enter the superior vena cava. Baccelli,[3] in 1863, first called attention to this possibility, although his explanation differed somewhat from that of Steele and Stengel. His idea was that the enlarged heart, by dragging the superior vena cava downward, carried with it the vena azygos major, thus drawing it tightly around the root of the lung and causing it to be compressed.

What has commended this theory to many is the fact that the vena azygos major receives as tributaries the intercostal veins of the greater portion of the right chest, vessels which drain the major portion of the right costal pleura. The natural assumption has been that with compression of this vein in its upper part there would result a venous stasis on the right side which would lead to a transudation. The theory has gained additional strength from the fact that these effusions are so frequently right-sided, or, when bilateral, greater on the right side. When the condition was bilateral the smaller, left-sided effusion was explained on the basis that the vena azygos minor, which drains less of the left chest than does the major of the right, and empties into the latter at the eighth or ninth thoracic

[1] University Medical Magazine, 1897; Journal of the American Medical Association, October, 1, 1904.

[2] University of Pennsylvania Medical Bulletin, 1901.

[3] Quoted by Steele, Jour. Amer. Med. Assoc., October 1, 1904.

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vertebra, would become affected only secondarily and hence to a slighter extent.

Every concrete theory hitherto advanced to explain the condition has been based on the assumption that the fluid is derived from the parietal pleura; and, of the vessels of this part of the membrane, the azygos veins have been held by most writers to be the source of the fluid. To this explanation five objections can be raised: (1) Only about two-thirds of the parietal membrane is drained by the azygos veins; (2) the collateral anastomoses of the azygos veins are so free and so numerous that, in the event of pressure, competent by-paths would soon be established and carry away any excess of fluid in the azygos radicles; (3) the vena azygos minor, emptying into the major, is subject to the same influences as the latter, and therefore the effusion should always be bilateral; (4) it is anatomically impossible for the heart, either directly or indirectly, to exert pressure upon the azygos major vein; (5) it does not explain left-sided effusions.

1. First, as to the azygos veins draining only about two-thirds of the parietal pleura. Like all serous membranes, the pleura consists of two portions, a parietal and a visceral, and the circulation in the two differs greatly, each receiving and discharging blood in vessels which belong to the structures with which the membrane is in contact. An example of this principle is afforded by the pericardium, of which the vessels of the parietal layer are derived from the thoracic aorta and the internal mammary, while those of the visceral layer or epicardium are branches of the coronaries. The pleura has a similar arrangement, but for the present the vessels of only the parietal layer will be considered. The arteries are derived from the superior and aortic intercostals, the internal mammary, the mediastinal, the œsophageal, the bronchial, and the phrenic, and the return circulation is through corresponding veins.

The most important thing to have clear in this connection is the vessels into which these veins drain. The intercostals vary somewhat at their vertebral ends, but the average arrangement is for the first intercostal on both right and left sides to empty into the innominate, while the second, third, and fourth on the right side form a trunk which opens into the vena azygos major, and the

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remainder on this side open separately into the same vessel. On the left side the second, third, and some times the fourth form a trunk, the superior intercostal vein, which opens above into the innominate and is connected with the left upper azygos vein. The intercostals from the fifth to the eighth on the left side form the left upper azygos and open into the azygos major or minor, while the remaining intercostals open individually into the azygos minor. At their sternal ends the upper nine or ten intercostals of both sides open freely into the internal mammary, or its musculophrenic tributary, the lower two or three having no such termination.

Of the remaining veins of the parietal pleura, the internal mammaries empty into the innominate, the mediastinal into the same place, the œsophageal into the azygos and also into the inferior thyroid and the gastric, the bronchial into the azygos, the inferior phrenic into the inferior vena cava, and the superior phrenic into the left innominate. The cervical pleura drains into the innominate, the posterolateral part of the right costal pleura into the azygos major, the upper third of the posterolateral part of the left costal pleura into the innominate above and the azygos minor below, and the lower two-thirds into the azygos minor. The anterior part of the costal pleura empties its blood into the internal mammaries, the mediastinal pleura into vessels which eventually reach the innominate and the portal, and the diaphragmatic pleura into veins which are tributary to the innominate and the inferior vena cava.

Analysis of this summary shows that the venous drainage of the parietal pleura is into widely separated vessels, and consists of veins which open into the azygos major and minor, the innominate, the inferior thyroid, the gastric, and the inferior vena cava. The deduction to be drawn from this is that while the azygos veins are of importance in carrying away the blood from the parietal pleura, only a portion of the membrane is drained by this system, perhaps not more than two-thirds.

2. Second, as to the numerous and wide anastomoses of the azygos veins. In order to render clear this portion of the discussion, it is perhaps advisable to give a brief resume of the tributaries and anastomoses of the azygos veins. The tributaries of the azygos major

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are the lumbar, the right intercostals with the exception of the first, the œsophageal, the posterior mediastinal, the venous plexus around the thoracic aorta, the posterior pericardiac, the bronchial, and the azygos minor. In connection with these vessels it is important to know how extensive and how practicable are their peripheral anastomoses. The azygos major begins just below the diaphragm, and at this point anastomoses with the right ascending lumbar vein, which connects it with the four right lumbar veins and, through the lowest of these, with the iliolumbar or the common iliac vein. The azygos minor has the same connections on the left side and by these anastomoses a ready side track into the inferior vena cava is established.

As regards the intercostals, "In the middle portion of their course the upper six or seven veins give off branches, the costo-axillary veins, which ascend toward the axilla and open into either the long thoracic or the thoracico-epigastric vein and so into the axillary, and, as it approaches the vertebral column behind, each vein receives a dorsal branch which accompanies the spinal branch of the intercostal artery and returns the blood from the skin and muscles of the back and also from the spinal column and its contents, this drainage being by means of a spinal branch which connects with the intervertebral veins."[1] "Laterally, at each intervertebral foramen the internal (spinal) plexuses send branches out from the spinal canal along the nerve trunks, and by means of these intervertebral veins, which have the form of plexuses at their origin and receive communicating branches from the external vertebral plexuses and from the veins of the spinal cord, the internal plexuses pour their blood into the vertebral, intercostal, lumbar, and lateral sacral veins, the connection with the intercostals being through their rami spinales."[2] In addition to these anastomoses the upper nine or ten intercostals open anteriorly into the musculophrenic or internal mammary veins. It is evident, therefore, that obstruction to the flow of blood through the intercostals would result in the blood seeking and finding other courses, which are many and wide, viz., the axillary, the vertebral, the lumbar and the lateral sacral.

The œsophageal veins anastomose with the inferior thyroid veins

[1] Piersol's Human Anatomy, p. 896.

[2] Ibid., p. 898.

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above and the gastric below. There are thus afforded paths into the innominate and the superior vena cava by way of the inferior thyroids and into the portal by way of the gastric. The posterior mediastinal veins open into the left innominate, and the destination of the plexus around the aorta is probably into the azygos and œsophageal veins. The posterior pericardiac veins anastomose freely with the anterior pericardiac, which open into the internal mammary, and through these a path is established into the left innominate or into the superior vena cava. The bronchial veins anastomose in the lung with some of the radicles of the pulmonary vein and thereby afford a wide open channel for any dammed back blood.

The vena azygos minor (vena hemiazygos) begins in the left upper abdomen and enters the thorax through the left crus of the diaphragm. Thence it ascends at the left side of the thoracic aorta and at the level of the eighth or ninth thoracic vertebra crosses to the left beneath the thoracic aorta and empties into the vena azygos major. The tributaries of this vessel are the ascending lumbar vein, the left lower four or five intercostals, the œsophageal, the posterior mediastinal, and occasionally the left upper azygos. The peripheral anastomoses of these vessels are, with the exception of the left upper azygos, the same as have been described in connection with the azygos major.

The left upper azygos vein (vena azygos minor superior, or accessory hemiazygos) begins at the second intercostal space on the left side and descends to the left of the middle line. At about the eighth thoracic vertebra it crosses to the right posterior to the aorta and œsophagus and anterior to the thoracic duct, to empty into the azygos major. Sometimes it empties into the vena azygos minor as the latter curves toward the right, and even when it empties into the azygos major it is frequently connected directly with the azygos minor. Its tributaries are the upper seven or eight intercostal veins, the left posterior bronchial veins, and a twig which connects it with the left innominate. The potentialities of these have been indicated in the description of the azygos major.

It would seem from this summary that the possibilities of a wide and ready collateral circulation through many by-paths, some leading

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into the superior and some into the inferior vena cava, are so great that it is almost unthinkable that any degree of obstruction could be sufficient to cause leakage into the pleural sac. In this connection it should be remembered that the pleura and its vessels are constantly subjected to a suction or negative pressure equivalent to 6 mm. of mercury, and must, therefore, be stronger and better equipped to resist pressure than any others in the body. Were this not so the pleural cavities of every one presenting the right blood conditions would fill with fluid until the pressure in the sac would be equal to the pressure within the lung.

In connection with the above resume of the azygos anastomoses it is interesting to note that Broadbent,[1] in referring to the pressure of aneurysms on the venous trunks, states that "there may be pressure on the azygos vein which passes up behind the root of the lung to open into the superior vena cava just before it enters the pericardium. This does not appear to give rise to any characteristic physical signs or symptoms, probably on account of the free anastomosis with the lumbar veins, which enables the blood to return without difficulty via the iliac veins and the inferior vena cava." This anastomosis mentioned by Broadbent is obviously but one of many.

3. Third, as to the vena azygos minor being subject to the same influences as the major. It will be remembered that the former vein, after receiving the left upper azygos, the lumbar, and the lower intercostal veins, crosses the vertebral column and empties into the azygos major. Being a tributary to the latter and the largest branch of the azygos tree, it must of necessity be subjected to the same pressure influences. Granting that obstruction at the azygos arch is responsible for these right-sided transudates, it is difficult to understand why the effusion should ever be limited to one side and especially the right, since stasis would first be manifest at the greatest distance from the point of pressure, viz., in the radicles of the vena azygos minor.

4. Fourth, as to the possibility of the heart exerting pressure upon the azygos major vein. In order to discuss this intelligently,

[1] Heart Disease, fourth edition, p. 445.

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a review of the course and relations of the vein is essential. The vena azygos major (vena azygos) begins in the right upper abdomen and passes into the thorax either through the aortic opening in the diaphragm or between the median and intermediate portions of the right crus. It ascends in the posterior mediastinum to the right of the median line, having behind it the right intercostal arteries and the bodies of the thoracic vertebræ. To its left lie the aorta, the œsophagus, and the thoracic duct. On reaching the level of the seventh thoracic vertebra it inclines slightly to the right, and at the level of the fifth or fourth bends forward and passes between the mesial surface of the right lung and the right aspect of the trachea at or just above the obtuse angle (155°) at which the right bronchus leaves the trachea. Either at or posterior to the plane of the anterior surface of the trachea it enters the superior vena cava just above the point at which the pericardium leaves the latter vessel. A number of measurements taken in the dissecting room of the University of Pennsylvania showed this point of entrance to be about 6 cm. above the entrance of the superior cava into the right auricle. The terminal portion of the vessel, as it arches over the right bronchus, is called the "azygos arch." Valves, usually to the number of four, are present in the vessel, but they are frequently unpaired and usually incompetent. In 22 per cent. the valves are absent.[1]

To justify the statement that the heart cannot press on the azygos major vein it is necessary to review briefly the anatomical relations at the roots of the lungs. These roots are made up of the bronchus, the pulmonary and bronchial vessels, nerves, lymphatics, and areolar tissue. The superior vena cava descends anterior to the root of the right lung to terminate in the upper portion of the right auricle, and this upper part of the auricle lies in an anterior relation to the root, an important fact, of which use will be made later. After leaving the vertebral column to course forward the azygos major passes in an arciform manner over the right pulmonary root to empty into the superior vena cava about 6 cm. above the termination of the latter in the right auricle. A dilated right heart, to exert

[1] Gruber, quoted by McMurrich in Piersol's Human Anatomy, p. 983.

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any pressure on the azygos arch, would necessarily displace upward and backward the pulmonary veins, the bronchus, the pulmonary

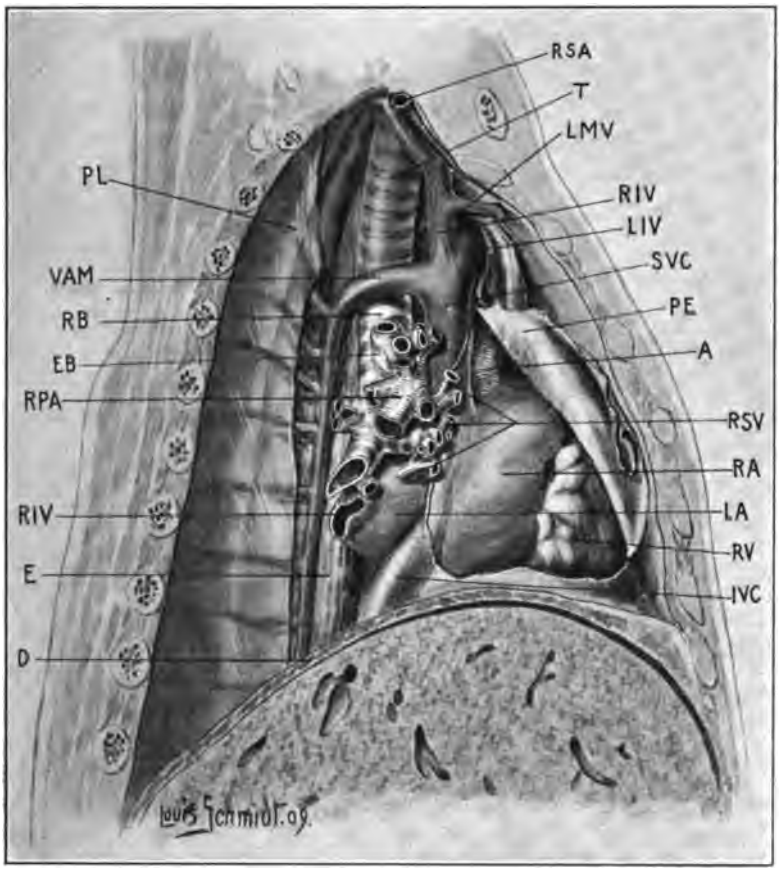

FIG. 1.—View from the right of the mediastinal contents and the root of the right lung: *D*, diaphragm; *E*, œsophagus; *RIV*, right inferior pulmonary vein; *RPA*, right pulmonary artery; *EB*, eparterial bronchus; *VAM*, vena azygos major; *PL*, pleura; *RSA*, right subclavian artery; *T*, trachea; *RMV*, right internal mammary vein; *RIV*, right innominate vein; *LIV*, left innominate vein; *SVC*, superior vena cava; *PE*, pericardium; *A*, aorta; *RVS*, right superior pulmonary vein; *RA*, right auricle; *LA*, left auricle; *RV*, right ventricle; *IVC*, inferior vena cava.

arteries, and all the minor elements in the lung root. To realize that this is an impossibility one has but to study the actual preparation made in a body where the viscera have been hardened in situ,

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and to take into consideration not only the intrinsic strength and resistance of these structures, but also their firmness of attachment. The ligamentum latum pulmonis alone, a firm reflection of the

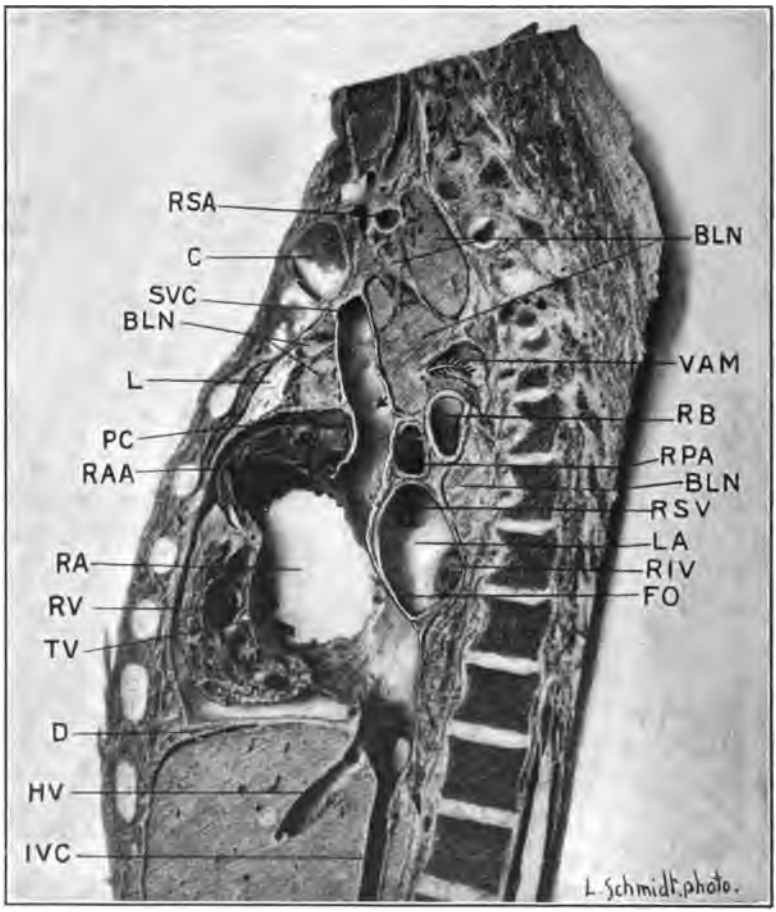

FIG. 2.—Anteroposterior section through the thorax in a plane 2 cm. to the right of the sternum: *IVC*, inferior vena cava; *HV*, hepatic vein; *D*, diagram; *TV*, tricuspid valve leaflet; *RV*, right ventricle; *RA*, right auricle; *RAA*, right auricular appendix; *PC*, pericardial chamber; *L*, lung; *BLN*, bronchial lymph nodes; *SVC*, superior vena cava; *C*, clavicle; *RSA*, right subclavian artery; *VAM*, vena azygos major; *RB*, right bronchus; *RPA*, right pulmonary artery; *RSV*, right superior pulmonary vein; *LA*, left auricle; *RIV*, right inferior pulmonary vein; *FO*, fossa ovalis.

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pleura connecting the lung root with the diaphragm, would be a potent factor in restraining any upward excursion of the bronchus and its associated structures. Study of the accompanying figures (Figs. 1 and 2) should convince one that the pressure claimed to be possible is out of the question. Theoretically there might be some direct pressure exerted by the heart upon the ascending part of the azygos, but cross-sections of the thorax (Fig. 3) show this to be impossible. The vein is so completely and well protected by the œsophagus and the aorta that such a contingency need not be considered.

Incidentally it might be stated that autopsy reports in which the assertion is made that the azygos major vein is dilated are, as a rule, untrustworthy. One writer (Steele[1]) states that he found this vein dilated "to the size of a goose quill." When one realizes that the normal diameter of this vessel is about 1 cm., it can readily be seen that such reports are untrustworthy. The average impression is that the azygos major is about the size of a radial artery, and many have been the expressions of amazement when our preparations have been shown to friends and the fact demonstrated that this vessel has at its upper end a normal caliber equal to that of a carotid or even a subclavian artery.

5. Fifth, as to the inability to satisfactorily explain why the effusion is, in a not inconsiderable number of cases, entirely confined to or much greater on the left side. Thus, of 108 cases recorded by Steele and Lord,[2] no less than 30 of them (27.7 per cent.) were left-sided, either entirely or to a great extent. Steele,[3] in his second paper, advanced the theory that this might be explained by the dilatation of the heart being greater on the left side than on the right. "In 11 cases of effusion confined to the left pleura, or greater on that side, the left heart, and especially the left ventricle, was especially mentioned as enlarged in 9 cases, that is, in four-fifths of the cases of left-sided effusion." He admits, however, that it is difficult to explain these cases on this theory, as there is no large venous trunk analogous to the vena azygos major to be compressed.

[1] Jour. Amer. Med. Assoc., October 1, 1904.
[2] Osler's Modern Medicine, vol. iii.
[3] Journal of the American Medical Association, October 1, 1904.

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He also mentions Rosenbach's explanation, namely, that the pressure exerted by the enlarged left ventricle on the left lower lobe produces atelectasis. As a result of long-continued congestion produced by collapse of the lung there arises a low grade inflammation of the pleura, and finally, an effusion forms in the pleural sac which

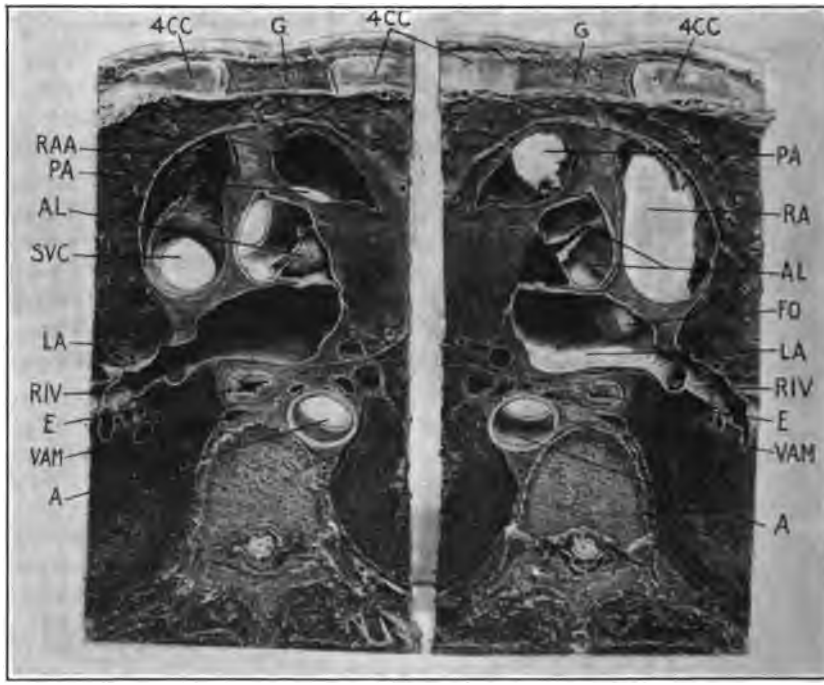

FIG. 3.—Lower (on the left) and upper (on the right) views of a transverse section through the mediastinal portion of the thorax at the level of the fourth costal cartilage: *A*, aorta; *VAM*, vena azygos major; *E*, œsophagus; *RIV*, right inferior pulmonary vein; *LA*, left auricle; *SVC*, superior vena cava; *AL*, aortic leaflets; *PA*, pulmonary artery; *RAA*, right auricular appendix; *ACC*, fourth costal cartilage; *G*, gladiolus; *RA*, right auricle; *FO*, fossa ovalis.

is partly transudate and partly inflammatory. Steele's comment on this is that his own "list of cases gives nothing to confirm or deny the theory of Rosenbach. I can only call attention to the fact that left-sided cardiac dilatation seems to bear some relation to left-sided pleural effusions."

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AUTHORS' EXPLANATION. The explanation which we wish to offer to account for these effusions is as follows: The fluid comes not from the parietal, but from the visceral pleura, and the outpouring is caused, so far as the pressure factor is concerned, by dilated portions of the heart pressing on and partly occluding the pulmonary veins.

Two sets of bloodvessels enter the lungs, the bronchial arteries and the pulmonary arteries. The former are nutritional in function and are derived from the aorta or from the first aortic intercostal. They enter the hilum of the lung and follow the posterior surface of the bronchi, some of their terminal branches reaching and supplying the pleura. The pulmonary arteries, in addition to carrying venous blood to the lungs, send twigs to the pleura. In this membrane there is a capillary anastomosis between the terminal branches of the bronchial and pulmonary arteries, on the one hand, and the venous radicles which are tributary, not to the bronchial, but to the pulmonary veins, on the other. This has been shown by Miller,[1] who says: "The capillary network into which the bronchial artery breaks up in the pleura gives rise to radicles which join the pulmonary vein." He also states: "I have failed to demonstrate by the use of granular injection masses any anastomosis between the bronchial and pulmonary arteries. On the other hand, by using injection masses which flow freely I have injected both sets of vessels (pulmonary artery and vein), but only by a backward flow (from the bronchial artery) of the injecting mass through the capillary network." It is evident, therefore, that the venous blood from the visceral pleura is poured into the pulmonary veins, and, as a corollary, that any obstruction to the flow through this vein, if of sufficient power and duration and accompanied by whatever condition of the blood which is essential to transudation, would produce leakage through the visceral pleura into the pleural sac.

Points in favor of our theory are that it explains equally well right-sided, left-sided, and bilateral collections of fluid, and also accounts for certain intrapulmonary conditions found clinically and postmortem in association with hydrothorax. Starting with

[1] American Journal of Anatomy, vii, 404, 405.

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the assumption that the transudate comes from the visceral pleura as a result of pressure on the pulmonary veins, a study of the anatomical relations between the heart and the roots of the lungs illumines the discrepancies which have long been noted. Anatomically the relations and pressure possibilities differ widely on the two sides.

The Anatomy of Right-sided Effusions. These are due to pressure exerted by a dilated right auricle upon the right pulmonary veins and upon the right end of the left auricle. That a dilated right auricle does press upon the right pulmonary veins is shown to be not only possible but inevitable by a study of the mutual relations of the right auricle and the right pulmonary root. It is shown with special clarity if the thoracic contents are hardened in position before the chest is opened. Studies under these conditions were made in three ways, by anteroposterior sections, a valuable method of studying thoracic relations which has been too much neglected, by transverse sections, and by lateral dissections of the mediastinum after removal of the lungs. The following facts were definitely brought out: Of the four chambers of the heart, three appear on the anterior surface and one on the posterior. The anterior cavities are, from right to left, the right auricle (the appendix mainly), the right ventricle, and the left ventricle, and all are plainly visible on anterior inspection. The main cavity or atrium of the left auricle is entirely a posterior structure (Figs. 2, 3, and 4), being invisible from the front, and it comes in relation anteriorly with the three other chambers as well as with the first portion of the aortic arch. Posteriorly it meets firm resistance and is separated from the bodies of the thoracic vertebræ by the contents of the posterior mediastinum, particularly the descending aorta and the œsophagus (Fig. 3). Above it is bounded throughout its entire length by the right pulmonary artery (Figs. 2 and 4), above which is the aortic arch. In front of its right-hand end, into which the right pulmonary veins open, are the right auricle and a little of the superior vena cava (Fig. 2), and in the lower portion of the interauricular wall is the thin fossa ovalis (Figs. 2 and 3), remaining from the foramen ovale.

If the right auricle were to become dilated it could expand forward but slightly, owing to the presence of the chest wall; it could not

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advance to the left on account of the right ventricle being there; below are the diaphragm and liver; above are the superior vena cava and an overlapping wedge of lung tissue. The path of least resistance is to the right, upward and backward, and in so expanding there would be inevitable compression of the structures which lie behind the right portion of the auricle. These are the right end of the left auricle and the root of the right lung (Figs. 1, 2, and 3). Of the component elements of the latter the most anterior are the pulmonary veins and behind these are the bronchi. The lower portion of the right end of the left auricle extends somewhat below the bronchus, and is bounded posteriorly by the œsophagus and anteriorly by the right auricle. In case; therefore, the latter expands, the two parts of the circulatory system which cannot escape compression are the right pulmonary veins and the right end of the left auricle, compression of the latter being facilitated by the thin fossa ovalis between the two auricles. The result of such compression would be stagnation in the right pulmonary veins and consequent leakage, on the outside, from the visceral pleura, and on the inside, into the lungs, the latter a point to be taken up later.

The Anatomy of Left-sided Effusions. The left auricle is unfortunately named, except in that the name indicates its physiological position. It is the posterior auricle, forming as it does the back surface of the heart, being the only portion of the heart to touch the posterior body wall and lying behind the three other cavities of the heart. It is a slightly flattened transversely placed cylinder with tributaries entering at both ends (Figs. 2 and 4). From its left upper anterior portion arises its auricular appendix (Fig. 4), which passes forward and curls around the left anterolateral aspect of the root of the pulmonary artery (Fig. 5). Posteriorly the appendix rests against the left upper pulmonary vein and anteriorly it comes close to the chest wall, from which it is separated only by pericardium and pleura and a small thin wedge of lung. Above, outside the pericardium, is the pulmonary artery, below is the left ventricle, and the only direction in which free expansion is possible is toward the left (Fig. 5). The left auricle is so hedged in on all sides that dilatation would first affect the appendix, which must act as a safety valve. The main cavity, or atrium, abuts firmly

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against the aorta, the œsophagus, and the vertebræ posteriorly (Fig. 3), and marked expansion in this direction would cause dysphagia from pressure on the œsophagus, a symptom not complained

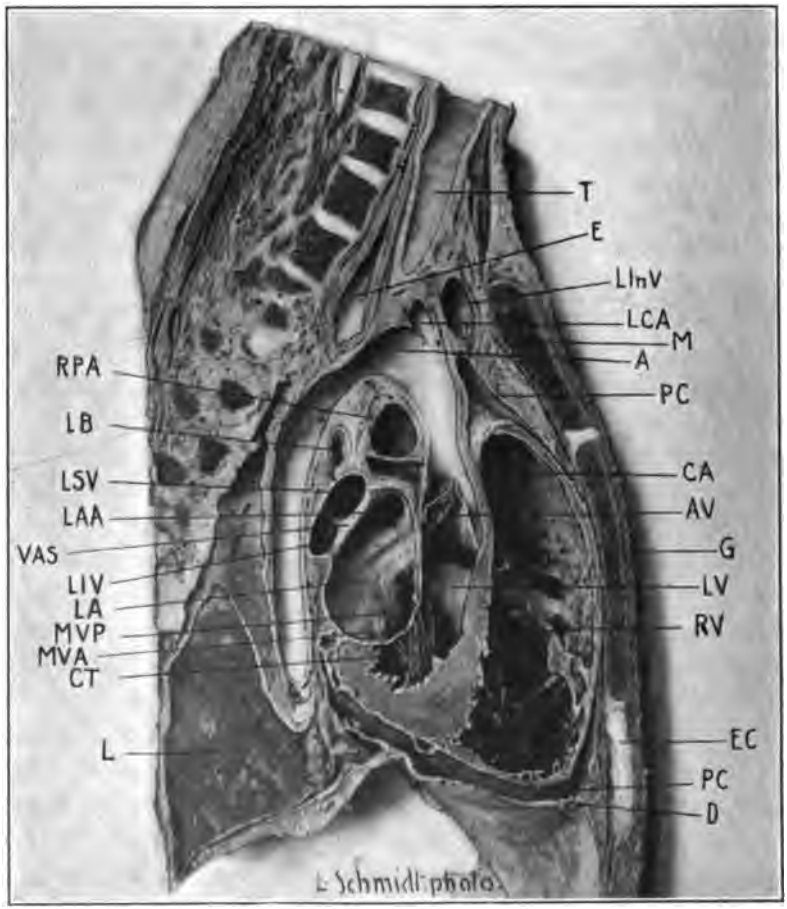

FIG. 4.—Median anteroposterior section through the thorax: *L*, lung; *CT*, chordæ tendineæ; *MVA*, mitral valve, anterior leaflet; *MVP*, mitral valve, posterior leaflet; *LA*, left auricle; *LIV*, left interior pulmonary vein; *VAS*, veno-appendicular septum; *LAA*, left auricular appendix; *LSV*, left superior pulmonary vein; *LB*, left bronchus; *RPA*, right pulmonary artery; *T*, trachea; *E*, œsophagus; *LInV*, left innominate vein; *LCA*, left common carotid artery; *M*, manubrium; *A*, aorta; *PC*, pericardial chamber; *CA*, conus arteriosus; *AV*, aortic valve leaflets; *G*, gladiolus; *LV*, left ventricle; *RV*, right ventricle; *EC*, ensiform cartilage; *D*, diaphragm.

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of in these conditions. In front are the other chambers of the heart, so placed that enlargement anteriorly would be prevented by the impinging of the anterior cavities against the chest wall. Upward

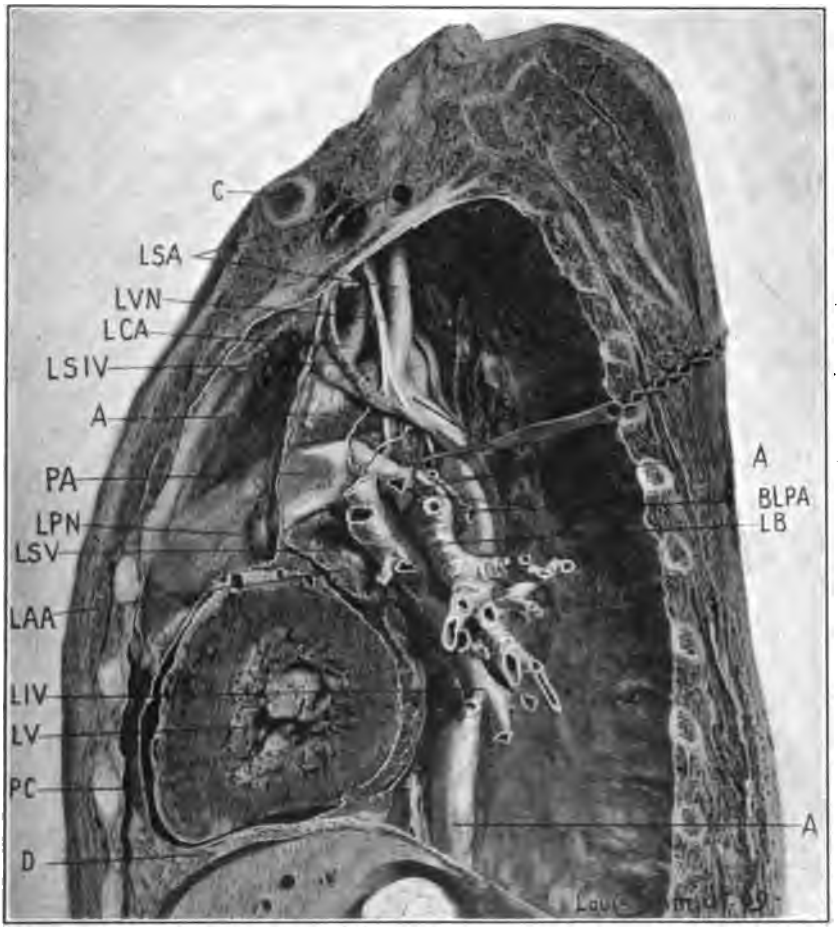

FIG. 5.—View from the left of the mediastinal contents and the root of the left lung (retouched photograph): *D*, diaphragm; *PC*, pericardial chamber; *LV*, left ventricle; *LIV*, left inferior pulmonary vein; *LAA*, left auricular appendix; *LSV*, left superior pulmonary vein; *LPN*, left phrenic nerve; *PA*, pulmonary artery; *A*, aorta; *LSIV*, left superior intercostal vein; *LCA*, left common carotid artery; *LVN*, left vagus nerve; *LSA*, left subclavian artery; *C*, clavicle; *A*, aorta; *BLPA*, branch of left pulmonary artery; *LB*, left bronchus.

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bulging would be blocked by the right pulmonary artery and the aortic arch, and below is the diaphragm, braced and supported by the liver. The natural expansile relief to overfilling would take place first to the left, and this would necessarily mean distention of the auricular appendix.

Occupying a position posterior and to the left of the appendix, separated from it only by the pericardium and the pleura, is the left upper pulmonary vein (Fig. 5). Behind, to the left, and in immediate contact with this vessel is the left bronchus (Fig. 5). Distention of the left appendix would necessarily squeeze the left upper pulmonary vein between the appendix and the bronchus and be a factor in causing transudation. The left lower pulmonary vein is in its extrapericardiac portion out of reach of the appendix, but it is so placed that dilatation of the left ventricle would involve the vein in compression between the ventricle and the bronchus (Fig. 5). In addition, there is in the left end of the left auricle a structure which may be a factor in left-sided effusions. This is the almost vertical partition, which might be called the veno-appendicular septum, between the opening into the auricle of the appendix anteriorly and the left pulmonary veins posteriorly (Fig. 4). A dilatation of the appendix which would thrust this septum backward would seriously hinder the flow of blood from the left pulmonary veins into the left auricle and be a factor in causing transudation from their radicles.

Greater frequency on the right side is due to the fact that dilatation of the right auricle is more common and more easy than a similar condition of the left side, and such dilatation is the only factor needed to cause damming back in the right pulmonary veins. On the left side, in order to include both upper and lower veins, there is needed dilatation of the left auricular appendix and of the left ventricle, with possibly a retrodisplacement of the vertical septum mentioned above, three factors as against one on the right side.

As far as we know, but one writer has come anywhere near the same conclusion as have we. West[1] in considering the various factors leading to hydrothorax states that "It is not agreed from

[1] Diseases of the Organs of Resp., ii, 757.

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which set of vessels the effusion comes, but I think it must be from the pulmonary artery or vein; and though the obstruction leads rather to edema of the lung than to pleuritic effusion, still the two are frequently associated together." And surely, if there is leakage from the pleura there should be a similar filtration into the lung tissue and air spaces, a condition which should cause changes in the breath sounds and the presence of moist rales. And if the latter part of West's statement is correct, viz., that œdema of the lung and pleural effusion are frequently associated, it would seem to bear out our theory as to the factors at work. And may it not be more than possible that the rales so frequently heard above an effusion and hitherto ascribed to compression of the lung, are due to intra-pulmonary leakage from the same pressure on the pulmonary veins that is causing the presence of the fluid in the pleural sac?

Recently one of us had the opportunity of studying a case of failing compensation in the service of Dr. H. A. Hare, in the Jefferson Hospital. There were found signs of a small effusion in the right chest, and the lung above the fluid was the seat of small moist rales. The other lung was absolutely clear. The fact that such cases as this are not uncommon would tend to lend support to the theory advanced in this paper.

Discussion.

Dr. W. M. L. Coplin: I am intensely interested in this extremely practical and illuminating presentation of certain facts with regard to hydrothorax. There is great difficulty in accepting any physical explanation; the growing tendency on the part of pathologists is to set aside increased venous pressure as an important element in the production of either edema of the tissues in general or of effusion into the serous cavities. Anyone seeing Fischer's experiments illustrating the colloidal theory of edema would be almost instantly converted to the belief that venous tension and capillary fulness are negligible quantities in explanation of effusion into serous cavities and of edema. There is hardly a pathologist who has not seen complete obstruction of a venous trunk in some particular area, with total absence of either edema or accumulation within any cavity

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drained. Hale White attacked, I think successfully, the theory that the ascites in cirrhosis of the liver is due to obstruction of the portal radicals within the contracting hepatic tissue. I exhibited before this Society a cancer of the liver, with what looked like complete obstruction of the portal vein due to thrombus, with secondary carcinomatous nodules throughout the liver, and at no time was there the least evidence of ascites. Complete occlusion of the vena cava without any edema of the drained vascular area is well known, and occlusion of the cava and the large trunks in the neck by extending thrombophlebitis, but without associated edema, has been observed; there is also to be considered the entirely familiar result, experimental and surgical, in which large veins have been ligated without the production of edema. There are other factors entirely aside from the physical explanations of these accumulations—some of them probably quite beyond our present accurate knowledge—probably primary chemical changes in the tissues that I regard as all-important. I had hoped to be able to present to the Society this year the results of some work which has been started on this subject. Dr. Funke, for me, has exhibited to the Society specimens of colloids showing the actions of organic and inorganic acids in the production of increased hygroscopic powers on the part of such substances. I produced on my own arm, following Fischer's methods, a series of edematous areas, but, so far as I could see the obstruction of the veins, did not in any instance hasten the appearance of the edema after injection of agents injurious to the colloids of the connective tissue. Last September, in talking this matter over with Dr. de Schweinitz, I called his attention to the necessity of a more extended study of the colloids in order to arrive at an explanation of papillo-edema, and suggested the possibility of such investigation yielding light concerning that obscure condition—glaucoma. At that time he regarded the suggestion an entirely novel one, but thought that changes in the colloids as a basis for retinal and papillo-edema might be a far superior and a better explanation than the so-called purely physical one. I do not believe edema will ever be clinically or pathologically explained upon the basis of heightened venous or capillary tension alone. Anyone seeing the intense pulmonary edema occurring in adrenalin experiments, the pleura often perfectly

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dry, must be skeptical in accepting heightened intrapulmonary tension as explaining pleural effusion. I have seen the lung as a sponge from which one could squeeze the water and with the pleura practically dry, although that is not the rule, of course. In autopsy on the human cadaver it is not at all an unknown thing, particularly in acute pulmonary edemas developing in the course of a few hours. It has been suggested that in venous retardation there occurs an accumulation within the tissues of one or more organic acids, and that these alter the colloids exactly as we might act upon them by the injection of organic acids, in either case increasing their capacity for taking up fluids. Among the most suggestive facts concerning this change in the tissues are those obtained by a study of the muscles of the lumbar region where large masses of edematous muscle can be removed in general anasarca. Proteolytic enzymes are contained in the edematous muscles of the lumbar region and similar enzymes are absent in the muscles of the anterior abdominal wall of the same cadaver. If this observation be correct, there must be back of any heightened tension explanation of edema some chemicophysiological basis for the edema. The more I study the question the more convinced I become that any purely physical explanation of edema based on heightened capillary or venous tension alone will not stand the criticism of modern methods.

Dr. David Riesman: I have been very much impressed by Dr. Fetterolf and Dr. Landis' paper, for it deals with a subject of great interest to clinicians. While inclined to agree with Dr. Coplin that pressure is not the only factor, I nevertheless believe that it is a factor and often determines the position of an effusion. In connection with mediastinal tumor, one frequently sees as an early and valuable sign a pleural effusion in the production of which mechanical pressure must be an important factor. The success of the Talma operation in relieving ascites in cirrhosis of the liver would also make one think that there is a good deal in the mechanical view. Whether the explanation given by Drs. Fetterolf and Landis is entirely adequate will have to be determined in the future. There are conditions which might not be explained by it. Thus, at the present time, there is under my care a young woman with mitral stenosis who has been tapped seven times for right-sided pleural effusion. Two

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days ago she was to have been tapped for the eighth time. I had examined her on the previous day and found an effusion up to the third interspace. When I came to tap her I discovered that the effusion had gone down a great deal and that the urgent dyspnea had subsided. As the treatment had not varied one would be inclined to think that some slight change in local pressure had brought about the unexpected change. In some instances the limitation of hydrothorax to one side may be due to an obliterative pleurisy on the opposite side.

DR. ALLEN J. SMITH: I wish to express the same view as Dr. Riesman as to the factor of blood pressure in the determination of pleural effusions, the possibility of any portion of the pleural area, whether visceral or parietal, as the part from which effusions may take place in increased amount. There is a second factor in the etiology of such fluid collections, namely, the rate of absorption, both by the bloodvessels and by the lymphatics of the entire pleural surface, visceral and parietal, both in the determination and localization of such dropsical collections; this fault may reside either in the condition of the membrane itself (as from dense thickening by a sclerotic pleurisy) or in some fault of the hemic or lymphatic vessels in the lung or in the diaphragm, chest wall, or mediastinum. The mere collection of fluid in such a cavity as a pleural sac may depend not merely upon the fact that it has been effused into the cavity, but as well because it has not been with sufficient readiness absorbed from such space.

DR. FETTEROLF, in closing: We are glad that Dr. Coplin emphasized the fact that pressure alone is insufficient to cause a transudate. This is a matter of common acceptance, and we were careful to bring out this point in the course of our paper. At the same time, while colloid or some other change may be and probably is necessary, the fact remains that one of the distinctive features of cardiac hydrothorax is its tendency to localize or preponderate on one side or the other, preferably the right. It is obvious that to explain these variations some anatomical factors should be sought, as there must be present local causes to account for localized transudates.

May, 1909.

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Active Bacterial Immunization in Animal Experimentation.

By B. A. THOMAS, M.D.

(From the William Pepper Laboratory of Clinical Medicine, University of Pennsylvania.)

Aside from the scientific study and interest, which is of increasing importance in this age of serum and bacterin therapy, relative to the nature of "opsonins" and their association or identity with amboceptors, complements, toxins, stimulins, agglutinins, precipitins, hemolysins, and what not, it seems indisputable that the blood serum contains certain antibodies, thermolabile and thermostabile, fundamental in the process of immunization, active or passive, possessing no mean grade of practical utility. This fact has been abundantly demonstrated, clinically, the past few years, in biological therapeutics of properly selected cases.

Denys and Leclef,[1] in 1895, experimenting with animals immunized against streptococci, were the first to produce reliable evidence that the serum of these animals contained bacteriotropic substances, possessing the power to sensitize streptococci, and hence render them susceptible to phagocytosis by the associated leukocytes. They demonstrated that the ability of an animal to overcome an infection depended, primarily, upon the direct influence of its serum, and only secondarily upon its leukocytes; moreover, that the latter were dependent upon the former for the commencement of their action.

Two years later Bordet[2] failed to confirm the conclusions of Denys and Leclef. Mennes[3] showed that phagocytosis occurred irrespective of the action of the leukocyte *per se*, but it remained for Wright and Douglas,[4] in 1903, and Neufeld and Rimpau,[5] in 1904, independently of the former, to thoroughly establish the fact that sensitizing antibodies do exist in the serum of the blood, and that phagocytosis is essentially dependent upon their influence on bacteria. These substances are the so-called "immune opsonins" of Wright and Douglas.

It is not my purpose, in this article, to enter into a discussion of the much-mooted question as to the nature or specificity of opsonins, but to report the demonstration or establishment, apparently at least, of a

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partial immunity in healthful rabbits by inoculation with certain bacterins or bacterial suspensions. This work was undertaken more than a year since in conjunction with Drs. Evans, Kneass, and Klaer, of the Pepper Laboratory, experimenting with hemolysins, agglutinins, and precipitins, in the hope of casting some additional light on the practical application and value of so-called opsonotherapy.

Bacterins were prepared from pure cultures of *Bacillus typhosus*, *Bacillus coli communis*, *Micrococcus aureus*, and *Bacillus tuberculosis* in the following manner: Five agar-agar test-tube cultural slants were made from each of the first three varieties of bacteria. Forty-eight hours later the growths from the five agar slants of each organism were washed off and suspended in a special sodium chloride solution, diluted up to 150 c.c. This suspension was thoroughly shaken to disintegrate any clumps into individual bacteria, and then submerged in a water bath and subjected to a temperature of 55° C. for forty-five minutes, and on the following day for one and one-half hours. The bacterins were then found to be ready for animal inoculation. A suspension of bovine tubercle bacilli was donated through the courtesy of Dr. John Reichel, of the Pennsylvania State Live Stock Sanitary Board. Dr. Reichel states, that they have determined definitely that five-sixths of the cultural growth from a bouillon flask is water, and that tubercle bacilli constitute constantly one-sixth by weight. A quantity of a tuberculous culture of low virulence was weighed and suspended in 0.85 per cent. salt solution, so that 1 c.c. should contain 1 mg. of *Bacillus tuberculosis*.

Five perfectly healthy rabbits, A, B, C, D, and E, were taken from stock. A was inoculated with 2 c.c. of *Bacillus typhosus* bacterin; B with 2 c.c. of *Bacillus coli communis* bacterin; C with 2 c.c. of *Micrococcus aureus* bacterin, and D with 1 c.c. of the suspension of tubercle bacilli. E was reserved for the control to furnish normal serum and leukocytes for determinations of opsonic indices from time to time.

The opsonic index of each animal was primarily determined for the particular bacterium, the bacterin or tubercle bacilli suspension of which he was subsequently to receive. Four inoculations were made, each time repeating the above-stated amounts at intervals of three to seven days. Each inoculation was preceded by the determination of the respective opsonic index.

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A review of the accompanying charts is almost self-explanatory. In I, II, and IV, it will be noted that the last inoculation was made on February 17, and although no bacterins were administered from this date until March 30, the time when the last index was taken, the curves plotted from the indices lie constantly in the positive phase, and in I, and in IV particularly, it would seem that the so-called high tide of immunity was being maintained. A study of these curves suggests

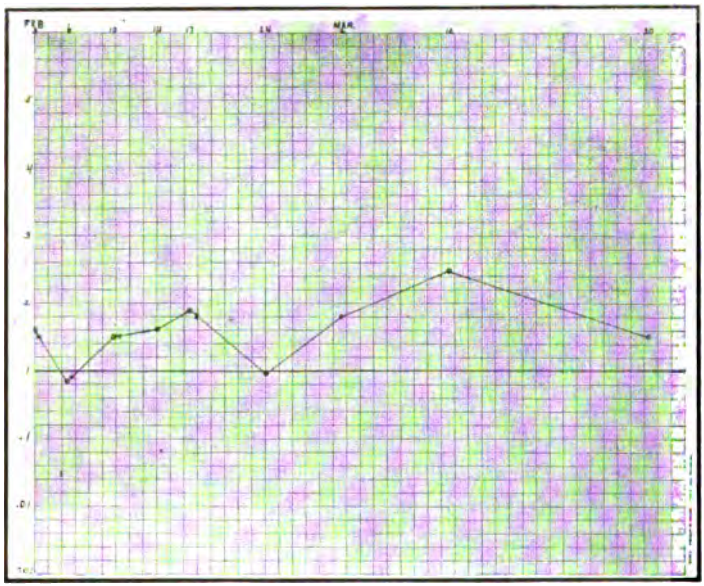

CHART I.—Curve of opsonic indices in rabbit *A*, representing immunization by *Bacillus typhosus* bacterin. *O*, opsonic index; *X*, inoculation with bacterin.

the interesting question as to the duration of time immunity can be expected to endure, after having been once established, following bacterial inoculation. It is quite satisfactorily determined, at least in the case of tuberculous infections, that the immunization following inoculation with living bacilli is much more lasting than with the dead organisms. This fact seems to be confirmed, or, at least, indicated, by my experiments. The solution of this problem is handcapped, owing to the fact that the idiosyncrasies and vital resistances of

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individuals vary considerably. Studies upon this subject will be reserved for future communications.

An interesting phenomenon may be observed in the case of rabbit C (see Chart III). As in the case of the other animals, the primary opsonic index of this rabbit for this particular bacterin was very close to the normal line. After a slight rise following the first inoculation, this animal, three days later, developed a suppuration of one eye, which steadily became worse and was associated with a tumor behind the

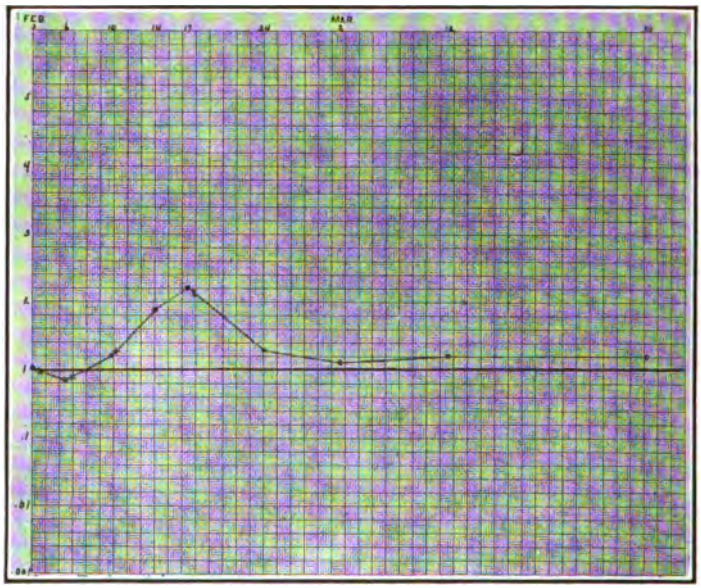

CHART II.—Curve of opsonic indices in rabbit *B*, representing immunization by *Bacillus coli communis* bacterin. *O*, opsonic index; *X*, inoculation with bacterin.

angle of the jaw. The health of the rabbit speedily declined, and he died two weeks after receiving the first inoculation, only three in all having been administered. Cultures from the eye suppuration showed the presence of a few cocci and bacilli arranged partly in chains, probably the result of air contamination. Microscopic examination of the tumor, which proved to be an enlarged lymph node, revealed only a simple adenitis. The feature in the opsonic curve of this rabbit is the steadily progressive tendency of the index in the direction of the

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negative phase, which was well borne out clinically by the serious ill-health of the animal, evidencing a minimum opsonic content of his blood serum.

A final glance at the charts in these experiments apparently demonstrate the following facts, if any reliance whatsoever can be placed upon the determination of the opsonic index, which, admittedly, at times, may lead to erroneous conclusions, but which here, in certain respects, at least, is associated with circumstantial evidence.

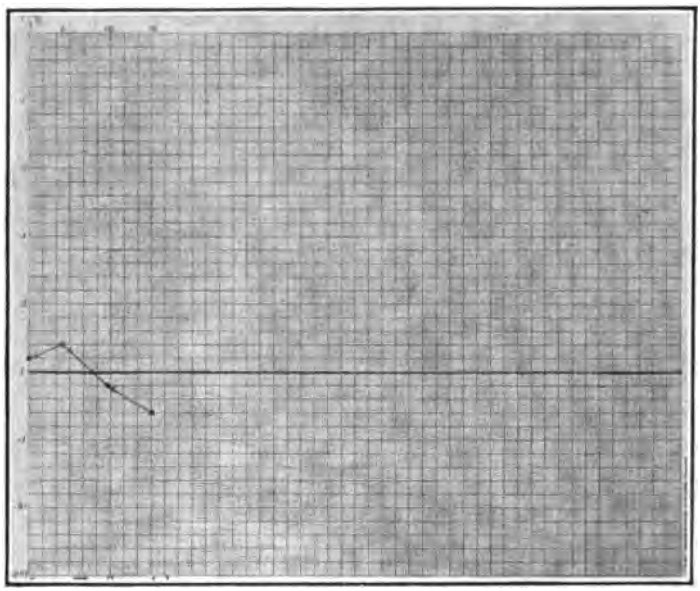

CHART III.—Curve of opsonic indices in rabbit *C*, representing immunization by *Micrococcus aureus* bacterin. *O*, opsonic index; *X*, inoculation with bacterin.

1. Bacterial immunization can be established in rabbits by inoculations of various bacterins.

2. The immunity endures for a period, the duration of which is as yet undetermined, but then declines.

3. The duration and degree of bacterial immunization by some bacterins or bacterial suspensions is more lasting than by others, notably, in this series, that by the suspension of tubercle bacilli, although absolutely properly sized and spaced inoculations might

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nullify these differences. This fact is, undoubtedly, more acceptably explained in rabbit D, by the inoculation with living organisms.

4. In the presence of a severe intercurrent infection, the opsonic content of the blood is markedly diminished.

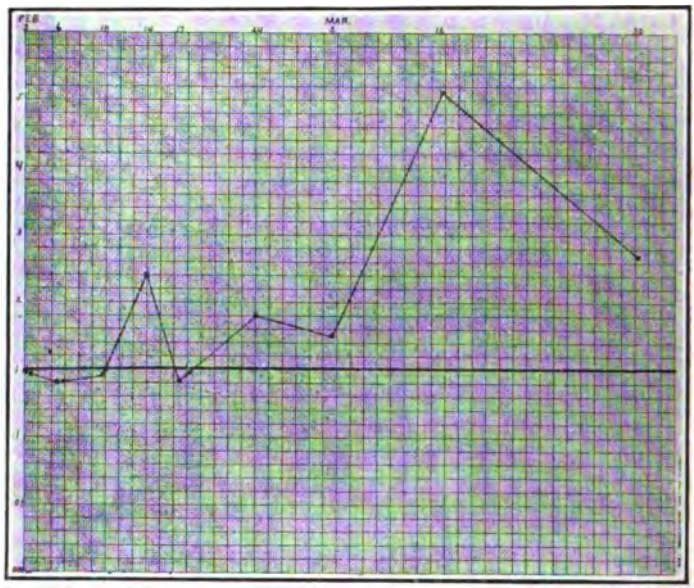

CHART IV.—Curve of opsonic indices in rabbit *D*, representing immunization by tuberculous suspension. *O*, opsonic index; *X*, inoculation with tuberculous suspension of low virulence.

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April 8, 1909.

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Preparation, Enthusiasm, and Self-sacrifice.[1]

By JOSEPH McFARLAND, M.D.

At the annual meeting of this Society held one year ago, following the dictates of our By-laws, I read a President's address containing a synoptical study of the work of the year; showed what had been done, explained why certain desirable improvements in the character of our work were difficult to achieve, and followed the retrospect by a brief statement of our future prospects.

You have honored me with the presidency a second time, for which I desire to express my sincere appreciation, and a second time it becomes my pleasant duty to formally address you at an annual meeting.

It is with satisfaction that I look back upon the work of this year, for in it I see much of profit and much pleasure. I feel that the Business Committee, through whose earnest efforts a succession of programs of surpassing interest was presented to you, and through whom you made the acquaintance of many distinguished guests, deserve the sincere thanks and commendation of the Society. I also feel that their successors, who are to be elected tonight, cannot do better than to find in the faithfulness of their predecessors an example and an inspiration.

The Society finds itself impoverished through the loss of two distinguished members, of both of whom it must be said that the grim spectre Death beckoned them all too soon. Dr. J. Alison Scott and Dr. Leonard Pearson were men who will be missed by all who knew them. In thinking of their lives, their work, their accomplishments, let us say, "Lord, keep our memories green!"

In reflecting upon my pleasant duty of this evening, I could not but feel that there was so little change in the general scope and character of our work that a second review of it, even though in accord with the letter of our law, must be so largely a repetition of what had gone before that it would lose much in the telling. At the risk of censure,

[1] Presidential Address delivered at the Annual Meeting of the Pathological Society of Philadelphia, October 14, 1909.

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therefore, I purpose to adopt an independent course, and endeavor to interest you in a few general thoughts upon certain recent advances in our knowledge of a disease long known, much dreaded, well studied, and well treated—*syphilis*.

It is a large subject, but I intend to be brief; it is a scientific subject, but I hope to be popular; it is a formal subject, but I hope to be familiar. If you look for information that may be new, you will not find it, for I shall merely use certain recent accessions of knowledge as texts for brief moralizing.

Until 1903 knowledge of this disease was purely clinical. It had been attained through painstaking observation made upon patients. How often does one of the present generation stop to ask himself how great was the difficulty of connecting the primary and secondary stages, and how much greater the difficulty of embracing a true conception of their relation to the tertiary stage? It took the great Hunter to arrive at a correct discrimination of the true "primary sore" to which we now give his name. Yet through the careful work of the clinician we learned all the facts of the disease, although its cause eluded us. We learned them so well that when the specific organism was finally discovered no important change of ideas came about in consequence of that event.

This is truly a monumental example of what the clinician can do! Let the bumptious graduate of modern institutions in which the laboratory is overemphasized sit up and take notice that there was science—accurate knowledge—in medicine several hundred years ago.

It was, however, impossible to arrive at a full knowledge of the disease for several reasons, and of these I wish to speak briefly.

1. *It was impossible to transmit it to the lower animals.* Now and again some patient investigator having applied the virus taken from a human lesion to a scarified or abraded animal membrane, thought he saw syphilis of a lower animal develop. In this manner a considerable literature accumulated in which, if you ever find time to review it, you will find reports of lesions so similar to those of human syphilis as to justify the experimenter in believing them to be such. But the only criterion upon which judgment of success or failure could be based was the clinical course of the experimental disease, and if

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there was no correspondence between it and that of the disease in man, it must be cast aside. Thus, it came about that experiments ceased or were sporadic in occurrence, and the conviction grew that the disease was one of human beings only.

If I felt justified in detaining you at the risk of wearying you, I would take time to recall to your minds that succession of gradual steps through which our thoughts ascended as our knowledge of physiology expanded, and we became acquainted with the principles of intoxication and immunity, stimulation and reaction, antibody formation, specific precipitates, and cytotoxins, and would pause when I reached the point at which Nuttall gathered the facts together and applied them biologically, so that the zoölogist came into possession of a new means of determining the "blood relationship" of animals.

It was upon the appearance of Nuttall's work that Metchnikoff and Roux, who had been making a preliminary survey of the subject, decided that if transmission of those diseases supposed to be peculiar to man was to be successfully accomplished in the lower animals only, it must be through attention to the principles of blood relationship.

Their actual experiments began in 1903, and in that year appeared the first of a series of memoirs entitled *Études expérimentales sur la syphilis.*

It was my good fortune to occupy a work place in the service of M. Metchnikoff at the Pasteur Institute, of Paris, during the time that the earlier experiments were in progress, and thus to be in a position to observe and follow them step by step. I had also the opportunity to learn much at first hand, and thus to become familiar with the thought, enthusiasm, and personal sacrifice of the two eminent investigators.

My acquaintance with these men was brief, but from them I learned some lessons never to be forgotten, and at the risk of your displeasure I shall digress once more from my chief topic and speak for a moment of those three conditions that above all others contribute to success in scientific work—*preparation*, *enthusiasm*, and *self-sacrifice.* In doing this I do not address myself to the older men of the Society who have learned wisdom by experience, and are as able to moralize as any other, but I turn for a moment to the younger contingent,

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whose more recent entrance upon the science of medicine has not yet brought them to a realization of its esoteric mysteries.

It is only through introspection and self-criticism that improvement becomes possible, and though it shocks and humiliates us to find ourselves inferior to others, there are times when these depressing emotions may be beneficial in influence. There are doubtless in our country many men who are as good as can be found in any, but to those who have worked in other countries and are familiar with the world's scientific literature there is an overwhelming preponderance of judgment in favor of the Europeans. Why should this be so? It seems to me to depend upon the more thorough preparation, the greater enthusiasm, and the more ready self-sacrifice of the European scientists.

It is with hesitation that I take upon myself the responsibility of criticising my compatriots and contemporaries, yet somehow I cannot help feeling that our comparative mediocrity may be referred to the lack of these three essentials to success.

Perhaps it is because we are a young nation; perhaps it is because we have no hereditary cast, the absence of which makes it possible for anyone to become an aristocrat who can get money; perhaps it is because we have little hereditary patience and complaisance, perhaps it is the all-pervading atmosphere of hustle and bustle in which we live; or perhaps it is because we have no recognized aristocracy of intellect—I do not know; but it seems to be the vice of Americans to seek to attain to knowledge by short cuts instead of by patient plodding, to enter upon investigation with little enthusiasm, as if lacking confidence in themselves, to look upon the work of others with suspicion born of their own sense of shortcoming, and to be unwilling to make personal sacrifices, especially financial sacrifices, that the ideal may be realized. Those fortunate enough to escape these vices stand out preëminently above their fellows, and as I point out what I believe to be our failings, their names and their works occur to you.

If the transmission of syphilis to the lower animals had met with signal failure, and if such failure depended upon inattention to the blood relationship of man and the animals employed, Metchnikoff and Roux determined to overcome this error by a series of experiments made upon animals whose blood relationship to man could

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be demonstrated, that is, the anthropoid apes. Here was the underlying scientific principle upon which the experiments were based.

But anthropoid apes were difficult to obtain and could be secured only at great cost, and when these grave savants sat down to consider the cost and the source from which the money was to come, we find their enthusiasm and self-sacrificing dispositions well exemplified by their determination to devote the proceeds of two large prizes awarded, one to each of them, for scientific work of superior excellence, the year before.

The first experiment was made upon a female chimpanzee, whose genitalia were scarified and a drop of serum expressed from a human chancre rubbed in. In twenty days a transparent oval vesicle surrounded by a red areola made its appearance. It soon flattened and became transformed to a slightly elevated and much indurated erosion. A few days later a marked enlargement of the inguinal lymph nodes of that side of the groin became apparent. The enlarged nodes were not tender, and were movable beneath the skin. At this time the animal was presented to the Academy of Medicine, examined by all of the members, among whom were Fournier, Castel, Hallopeau, and Marc Sée, all of whom pronounced the lesion to be a true indurated chancre.

Just one month after the appearance of the chancre—fifty-six days after the first inoculation—disseminated papules appeared upon the anterior and posterior surfaces of the thorax, increasing in number during the following fifteen days. The papules were dry and scaly, rounded in shape, of various sizes, and surrounded by a reddened zone. The skin covering them softened and a crust gradually formed, and their resemblance to the secondary eruptions in man became more and more distinct. In about three months the animal showed much malaise; its health was evidently much impaired. Forty-nine days after the appearance of the secondaries the animal died of acute pneumococcus infection, and the experiment came to an untimely termination.

This was the beginning of a notable series of animal inoculations continued by Metchnikoff and Roux and many others, so that, especially in the East, where orang-outangs were available, much experimentation of confirmatory character was performed. From the

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chimpanzee and orang-outang it was found that the virus could be successfully implanted to macacus, and from this to lower monkeys, but the farther from blood relationship with man the experiment animal was removed the less characteristic and less severe were the results of the inoculations.

It is a pleasure to recall the importance of that first chimpanzee. Never was a monkey so distinguished by the attentions of scientific men! How vividly I recall old "Père Metch," tall, slightly stooped, his long, dark hair slightly streaked with silver falling about his shoulders, his penetrating eyes peering through steel-rimmed spectacles, and his bearded face full of quiet thoughtfulness or burning animation as he returned from his daily visit to his monkey.

Sometimes there would be with him a French exquisite, dressed *a la mode*, with a shiny top hat upon his silvered head and the corners of his white moustache tightly twisted into points, who talked animatedly, gesticulating with his hands in typical French fashion—probably Fournier, at least so I was told.

In these early experiments you may have remarked that though it was in the laboratory that the means of success were evolved, it was the clinician who was called upon to make the diagnosis and to confirm the success of the experiment—another triumph of clinical observation. But this relationship of the clinician to the laboratory was soon to be reversed through the new and more important discovery of the specific organism. Of course, Metchnikoff and Roux hoped—I think I may say expected—that this should be their next achievement, but it was reserved for another, and therein they sustained a bitter disappointment, though let it be said to their credit that they were among the very first to confirm it when it came about.

2. *It was impossible to recognize the specific cause of the disease.* It would, indeed, be a wearisome hour for you, should I take your time to review those attempts at finding the cause of syphilis that spread themselves over many pages and through many years of bacteriological literature. The few that received more than momentary attention—Lustgarten, von Niessen, and Siegel—are now doomed to early oblivion. Like many other worthy men, they did their best, but were mistaken.

The honor fell to a young German, Fritz Schaudinn, who with his

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associate Hoffmann published his observations in the *Deutsche medizinische Wochenschrift*, May 4, 1905. By the use of the Giemsa method of staining they had been able to find, in serum expressed from venereal sores, two forms of spiral organisms, one very common in occurrence, the larger of the two, easily stained and quickly recognized, probably already described by others, but to which they applied the name *Spirocheta refringens;* the other smaller, more tightly coiled, scarcely stained though similarly exposed to the reagents, and found only in clinical syphilis, the *Spirocheta pallida.* This their many observations led them to believe was the true specific organism.

The announcement received enthusiastic attention, and was speedily confirmed in all parts of the world, one of the most important confirmations coming from Metchnikoff and Roux, who found it in the lesions of their experiment animals. An enormous literature quickly appeared, the earlier part of which was ably reviewed before this Society by Dr. Rosenberger.

At first there were doubts in the minds of some and misinterpretations in the thoughts of others, but time has eliminated them all, and at present we have nothing but confirmatory contributions upon the etiological significance of the organism. The improvement in the technique of staining and the introduction of the silver impregnation method of staining the organism in the tissues by Levaditi and Manouelian made possible the pursuit of the organism as it passed from the seat of original inoculation to deeper and deeper structures, and through the placenta to the fetus, where it occurs in enormous numbers, so that we are now able to state with positiveness that the occurrence and distribution of this organism shows a perfect correspondence with the clinical course and progress of the disease.

Thus, it is found in the serum expressed from the chancre; it is found in the juice extracted from the enlarged lymphatics, and in sections made of these lesions is found both in and between the cells of the tissues. At the time of the appearance of the secondaries it has been found in the circulating blood. It is found in blood expressed from the roseola of the secondary stage, and in sections of all of the secondary lesions. It is found in large numbers in the syphilitic placenta, and in enormous numbers in the tissues of the congenitally

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syphilitic fetus and in the lesions of congenitally syphilitic infants. It is found in all of the lesions of syphilitic apes and monkeys and in the corneal ulcerations of experimentally infected rabbits. It is extremely rare in the lesions of tertiary syphilis, both the sclerosis and the gumma.

With this accession of knowledge came about the already mentioned reversal of the relationship of the clinician and pathologist. At first the laboratory man was obliged to appeal to the clinician to confirm the results of his experiments; now the clinician is compelled to seek the aid of the laboratory man to sustain his doubtful diagnosis.

The criterion of the disease is changed. It is no longer a combination or succession of symptoms that establish the diagnosis, for this is possible only when they are sufficiently characteristic; it is the presence of the *Treponema pallidum* that proves the case. This criterion applies equally well to human and comparative cases. When one inoculates a lower animal and produces a lesion, the question of the syphilitic or non-syphilitic character of the lesions is no longer determined by patiently waiting for results that may not come or by clinical correspondence with the disease in man, but is immediately determined by an examination of some serum from the lesion with a dark field illuminator or by the staining and demonstration of the specific organism.

By such means the syphilitic nature of the lesions in apes and monkeys has been established, the corneal ulcerations of rabbits likewise established, but the vague lesions of swine, guinea-pigs, mice, rats, and frogs rejected.

3. *There is a period in the course of the disease when there are no clinical manifestations and during which the specific organism cannot be found.* This circumstance was a source of constant embarrassment to the clinician who had no means of determining the state of recovery, partial recovery, or mere latency of disease, that followed his course of treatment. Patients thinking themselves cured gradually fell into a distressing condition through the appearance of the tertiary symptoms, and on all sides there were cases of well-recognized disease the origin of which is unknown, though the frequency with which syphilis appears in their medical history is so suspicious a circumstance that it has gradually been accepted as their cause. No

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clinical knowledge enabled one to foretell what would happen to the patient after the lapse of this intermediate period, nor could the discovery of the microörganism be appealed to, since it had disappeared not to reappear in the future lesions of the tertiary stage.

And now comes the Wassermann-Neisser-Bruck discovery of a method of recognizing the disease during this particular stage. It is a refinement of physiological chemistry probably destined to play a conspicuous role in the future medical diagnosis.

Although the original contribution appeared no longer ago than 1906 (Eine serodiagnostische Reaktion by Syphilis, *Deut. med. Woch.*, 1906, No. 19), a large literature has already appeared and the method has undergone simplification and improvement.

The test appears to be extremely complicated to those who have not used it, because a number of reagents must be employed each of which is difficult to obtain. When all of these are readily available the test itself is simple. This means that certain men must devote themselves to this particular work, have the necessary materials at hand, acquire the requisite skill, be ready at any time to make the test, and because of their skill and experience be prepared to furnish a reliable judgment upon the reaction obtained.

The test, as you know, was originally made by combining an extract of a congenitally syphilitic liver, the previously heated cerebrospinal fluid of the patient under examination, and the fresh, unheated serum of a guinea-pig. This combination was supposed to embrace (1) microörganismal substance in the liver extract, (2) specific amboceptors in the cerebrospinal fluid, and (3) complement in the normal guinea-pig serum. If the patient was normal and the heated cerebrospinal fluid contained no syphilitic amboceptors, no reaction took place and the complement in the guinea-pig's serum remained free, so that when the mixture received the further addition of some washed blood corpuscles and some hemolytic serum, with a specific affinity for those corpuscles, the free complement, the hemolytic amboceptors, and the corpuscles immediately combined, with resulting hemolysis. If, however, the patient was syphilitic and the heated cerebrospinal fluid contained specific syphilitic amboceptors, so soon as the liver extract, the heated cerebrospinal fluid, and the normal unheated guinea-pig's serum were brought together the complement

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attached itself to the amboceptors and they to the microörganismal substance, the complement became anchored, no free complement remained in the mixture, and when blood corpuscles and their specific hemolytic serum was subsequently added there was no hemolysis because the complement was missing.

This was the original theory and practice. It soon became modified by the substitution of the serum for the cerebrospinal fluid of the patient to be examined, by the employment of an alcoholic extract instead of a fresh liver extract, and later was further modified by the use of normal liver extract or of lecithin instead of the syphilitic liver, as first suggested.

But you are thinking that this last modification undermines the scientific foundation of the theory, for it was based upon the assumption that the congenitally syphilitic liver contained microörganismal substance, by whose presence in the primary mixture the specific syphilitic amboceptors and the complement became anchored. This is, indeed, true. The theory was wrong, but the practice was right. We mistook the exact nature of the reaction, but it is a reaction just the same, and one accurate in the hands of different experimenters within a margin of from 5 to 10 per cent.

As modified, the test has become a comparatively simple one in the hands of a skilled workman, and enough investigation has been performed to give us approximately 90 per cent. of accuracy in determining the condition of a patient concerning whom clinical examination and observation can reveal nothing. The sole reliance of the clinician in the past was the so-called "therapeutic test," not so bad, perhaps, when it succeeded, but most unpleasant in its consequences when it failed.

We are thus in a position to acquire accurate information of the condition of a patient the nature of whose past illness may be unknown to himself; of a patient who may wilfully deceive his medical adviser; and of those patients whose past history points to syphilis as the source of their present troubles, the ataxics and paretics that fill our hospitals.

It is too soon for us to know how far-reaching may be the influence of these recent discoveries, but it seems justifiable to believe that when they make possible an immediate and certain diagnosis, when they

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enable one to determine the latency of the inactive disease, they must be destined to occasion an enormous improvement in the thoroughness with which the disease will be treated, and hence the alleviation of much of the suffering that obtains at the present time.

4. *The microörganism cannot be cultivated artificially, so that immunity experiments in the nature of therapeutic serums and bacterio-vaccines are at present impossible.* This is the problem the future solution of which must bring distinction to whomsoever achieves it. Who shall it be?

I may not close this address without dwelling upon the reciprocal relations of the clinician and the biologist. The former has spent centuries in acquiring knowledge that the latter is perfecting; the latter is working out exact methods whose applications must in the future perfect the work of the former. Neither can satisfactorily perform the work of the other, neither can do the work of both, for the field is too large. Monuments to the glory of clinicians cover the pages of medical history. The future opens its doors to the laboratory man to whom her laurels must be awarded.

Some of us harp continually upon that string which declares that the future hope of medicine is centred about the laboratories, some sound the note of caution and sing the undying fame of the clinical work of all ages; both notes are thin and discordant, and it were better to learn the harmonious chords in which the clinic and the laboratory may be combined in purpose.

Of the three additions to knowledge discussed in this rambling discourse, each has come from a laboratory and been the work of laboratory men; each can be definitely traced to antecedent work done in the laboratories by laboratory men. I am sure you must agree with me that the much needed discovery of methods of isolating and cultivating the *Treponema pallidum* by which will be made possible further experiments in immunization and specific therapy, can only be expected to come from a laboratory and to be the work of a laboratory man.

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WHEREAS, We have heard with profound regret the announcement of the death of DR. GEORGE C. HARLAN, for fifty-two years a member of this Society; therefore be it

Resolved, That the Pathological Society feels the loss of a member who was not only active in the founding of the Society, prominent in its early growth and development, but who also in his later years reflected on it much honor by a life devoted tc scientific and careful work in his chosen specialty; and be it further

Resolved, That these resolutions be entered in the minutes, printed in the PROCEEDINGS of the Society, and a copy of the same be sent to his family.

JOSEPH SAILER,
GEORGE P. MULLER,
FRED H. KLAER.

WHEREAS, In the death of DR. LEONARD PEARSON there has been lost to science a worker widely and honorably known; to this State and community an untiring, efficient, and sound-minded medical official; to his profession and school a warm-hearted, sympathetic, and beloved colleague and teacher; and to this organization an associate whose membership had reflected honor upon the Society and whose participation in our work was uniformly profitable, illuminating, and inspiring. Typifying in ideal manner the dignified modesty of the truly great, he has by his force of character, his spirit of advancement, his readiness to serve, and his innate and great ability, proved his right to be specially honored by those who have known him; therefore be it

Resolved by the Pathological Society of Philadelphia to set aside a page in its records for this minute, expressive of our sense of loss in the death of DR. LEONARD PEARSON, our sincere sorrow, and our sympathy with his dear ones in their bereavement.

W. M. L. COPLIN,
ALLEN J. SMITH,
JOSEPH MCFARLAND.

WHEREAS, In the death of DR. J. ALISON SCOTT this Society has lost one of its members whose association has for years aided in the upholding and progress of its best interests and work, whose engaging personality, simple dignity, and acknowledged ability were inspirational to all those who knew him and were co-workers with him, whose methods of study and of practice made him easily a leader in our profession; therefore be it

Resolved, That in testimony of our heart-felt sorrow for his death, our respect for his memory, and our sympathy for his family, this statement be inscribed in the Minute Book of the Pathological Society of Philadelphia and published in the PROCEEDINGS of the Society, a copy being sent to the family of DR. SCOTT.

W. M. L. COPLIN,
ALLEN J. SMITH,
JOSEPH MCFARLAND

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